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Natriuretic Peptides in Valvular Heart Disease

Thesis submitted in accordance with the requirements of the University of Edinburgh for the degree of Doctor of Medicine

by

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AUTHOR'S DECLARATION

This thesis represents research undertaken at Middlemore Hospital and Green Lane Cardiovascular Unit, Auckland, New Zealand and supervised by Professor Newby at the Centre for Cardiovascular Science, University of Edinburgh, United Kingdom. I certify that this thesis has been composed by me and that I have made a substantial contribution to this research as part of a research group. I am grateful for the assistance of colleagues and their contribution has been formally acknowledged. Much of this work has been published in peer-reviewed journals as outlined in the bibliography. The material contained in the thesis has not been presented, nor is currently being presented, either wholly or in part for any other qualification.

Dr Vishal Sharma, MB ChB, FESC, FRCP Edin December 2015

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ABSTRACT

Plasma natriuretic peptide concentrations rise in response to either atrial or ventricular wall stretch and have been found to be useful in the diagnosis and assessment of patients with congestive cardiac failure. Although previous studies have suggested that plasma natriuretic peptides may offer some prognostic information in patients with valvular heart disease, it is unclear whether concentrations reflect disease severity and how plasma concentrations vary across different valve lesions. The aim of this research was to identify the factors that affect natriuretic peptide releases in valvular heart disease (VHD) and to investigate whether natriuretic peptides can be used in clinical practice to identify those patients who may benefit from early intervention.

Plasma brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) concentrations were measured in patients with normal left ventricular (LV) systolic function and isolated VHD (mitral regurgitation, MR, n=33; aortic regurgitation, AR, n=39; aortic stenosis, AS, n=34; mitral stenosis, MS, n=30), and age and sex matched controls (n=39) immediately prior to exercise stress echocardiography. Peptide levels were compared against age and sex matched controls and against markers of severity for each valve lesions and across different valve lesions.

Compared to controls, patients with all types of VHD had elevated plasma BNP concentrations [(MR median 35(inter quartile range 23-52), AR 34(22-45), AS 31(22-60), MS 58(34-90); controls 24(16-33) pg/mL; $p<0.01$ for all]. LV end

diastolic volume index varied by valve lesion; [MR (mean ± standard deviation 77±14), AR (91±28), AS (50±17), MS (43±11), controls (52±13) mL/m^2; p<0.0001]. There were no associations between LV volume and BNP. Left atrial (LA) area index varied [MR (18±4cm^2/m^2), AR (12±2), AS (11±3), MS (19±6), controls (11±2); p<0.0001], but correlated with plasma BNP concentrations: MR (r=0.42,p=0.02), MS (r=0.86,p<0.0001), AR (r=0.53,p=0.001), AS (r=0.52, p=0.002). Higher plasma BNP concentrations were associated with increased pulmonary artery pressure and reduced exercise capacity. Despite adverse cardiac remodelling, 81(60%) patients had a BNP concentration within the normal range. In patients with MS BNP was strongly associated with left atrial area index (r=0.86; p<0.0001) and a BNP level of greater than 2 times the upper limit of normal identified patients who fulfilled guideline criteria for intervention (Area under the curve (AUC) 0.87 [0.74,0.99], p =0.006) and lower exercise capacity (AUC 0.82 [0.67,0.97]; p=0.004). In AR patients significant remodelling could occur whilst BNP remained within the normal range and in general BNP appeared less useful in assessing disease severity. However raised levels of BNP was associated with more severe AR as assessed by left ventricular outflow tract:AR Jet area ratio (r=0.43 p=0.0007). AR patients with an abnormal BNP had signs of early LV dysfunction on exercise with a lower LV longitudinal strain rate post exercise compared to AR patients with a normal BNP (0.68±0.31 vs. 1.06±0.45 1/sec; p=0.02). In MR patients, higher plasma BNP concentrations were associated with larger left atrial area index (r=0.42, p=0.02), higher pulmonary artery pressure (r=0.53, p=0.002) and a lower exercise time (r=-0.60, p=0.0002). BNP was not associated with any marker of left ventricular size or function in MR.

These findings suggest that despite significant LV remodelling, plasma BNP concentrations are often normal in patients with VHD. Consequently, plasma BNP concentrations should be interpreted with caution when assessing patients with VHD. However natriuretic peptide levels offer complementary information to the standard assessment of patients with VHD and an unexplained finding of an elevated BNP in an otherwise asymptomatic patient should prompt further investigation.

CONTENTS

LIST OF ABBREVIATIONS

2D	2-Dimensional
3D	3-Dimensional
A	Late Diastolic Filling Velocity
ACC	American College Of Cardiology
AF	Atrial Fibrillation
AHA	American Heart Association
ANOVA	Analysis Of Variance
ANP	Atrial Natriuretic Peptide
AR	Aortic Regurgitation
AS	Aortic Stenosis
ASE	American Society Of Echocardiography
AUC	Area Under The Curve
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CABG	Coronary Artery Bypass Grafting
CR	Contractile Reserve
CW	Continuous Wave Doppler
DD	End-Diastolic Dimension
E	Early Diastolic Filling Velocity
E'	Early Annular Velocity
EAE	European Association Of Echocardiography
ECG	Electrocardiogram

EDTA	Ethylene Diamine Tetraacetic Acid
EF	Ejection Fraction
EROA	Effective Regurgitant Orifice Area
ESC	European Society Of Cardiology
HPLC	High Performance Liquid Chromatography
HSD	Honest Significant Difference
ICC	Intraclass Correlation Coefficients
LA	Left Atrial
LAAI	Left Atrial Area Index
LV	Left Ventricular
LVEDVI	Left Ventricular End-Diastolic Volume Index
LVEF	Left Ventricular Ejection Fraction
LVESVI	Left Ventricular End-Diastolic Volume Index
LVIDs	Left Ventricular Internal Dimension Systole
LVOT	Left Ventricular Outflow Tract
MET	Metabolic Equivalents
MG	Mean Gradient
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
MS	Mitral Stenosis
MV	Mitral Valve
MVA	Mitral Valve Area
MVR	Mitral Valve Replacment.
NL	Nyquist Limit
NP	Natruretic Peptides
NT pro ANP	N-Terminal Pro-Atrial Natriuretic Peptide
NT pro BNP	N-Terminal Pro-Brain Natriuretic Peptide

NYHA	New York Heart Association
PAP	Pulmonary Artery Pressure.
PCWP	Pulmonary Capillary Wedge Pressure
PHT	Pressure-Half Time
PISA	Proximal Iso-Velocity Surface Area
PLAX	Parasternal Long Axis
PM	Papillary Muscle
PMBV	Percutaneous Mitral Balloon Valvotomy
PW	Pulse Wave Doppler
RV	Right Ventricular
RVd	Right Ventricular Diastolic
RVG	Radionuclide Ventriculography
RVSP	Right Ventricular Systolic Pressure
S'	Systolic Annular Velocity
SBP	Systolic Blood Pressure
SD	End-Systolic Dimension
TFA	Trifluroacetic Acid
TR	Tricuspid Regurgitation
VHD	Valvular Heart Disease
VTI	Velocity Time Integral

CHAPTER ONE

INTRODUCTION: VALVULAR HEART DISEASE, ECHOCARDIOGRAPHY AND NATRURETIC PEPTIDES

1.1 VALVULAR HEART DISEASE

Valvular heart disease remains a common cause of cardiovascular mortality and morbidity worldwide. The development of acute valvular lesions such as acute mitral regurgitation secondary to a ruptured chordae or acute aortic regurgitation secondary to aortic dissection are usually poorly tolerated and present with signs of severe acute heart failure. Patients presenting with acute valvular lesions often need to be managed by relatively urgent or even emergency cardiac surgery to prevent death.

In contrast however, patients with chronic valve disease often remain asymptomatic for many years. Valvular heart disease (VHD) results in abnormal pressure and/or volume load on the heart and a number of compensatory changes may occur in response to this. Previous studies have identified that once patients become symptomatic, their survival without surgery to repair the valve defect is poor [Delahaye *et al* 1991, Horstkotte and Loogen 1988, Klodas *et al* 1997, Ross and Braunwald 1968, Wood 1954]. Consequently the presence of symptoms is a key feature in the assessment of patients with VHD and their presence is a strong factor when considering intervention or valve surgery in the current guidelines for the management of patients with VHD [Bonow *et al* 2006, Nishimura *et al* 2014].

However due to the often slowly progressive nature of VHD, defining the exact onset of symptoms in patients with VHD can be difficult. In addition many patients who remain asymptomatic can develop significant dilatation of cardiac chambers and occasionally impairment of ventricular function or pulmonary hypertension prior to

the development of overt symptoms. These patients are at increased risk of perioperative complications at the time of surgery and in some cases the heart size and function may not return to normal levels of function post-operatively. Conversely operating on patients too early (unless the valve is repairable) has the consequence of patients having an artificial heart valve in situ for a longer period. In the case of mechanical heart valves this is associated with a 1-2% risk per annum of complications and in the case of a biological valve increases the likelihood that further valve replacement will be necessary assuming the patient has a reasonable life expectancy. Consequently early diagnosis, regular follow- up and careful timing or referral for cardiac surgery is essential to optimally manage patients with valve disease.

1.1.1 DIAGNOSIS AND ASSESSMENT OF VALVULAR HEART DISEASE

In the normal heart, blood flow through the heart valves is relatively laminar and consequently relatively silent on auscultation except in haemodynamically active states. However valve abnormalities such as stenotic or regurgitant jets result in turbulent high velocity flow. This results in audible murmurs that have typical characteristics depending on the underlying heart lesion. Consequently cardiac auscultation remains an important part of cardiac screening and assessment for heart valve disease and in many parts of the world it still remains the only readily available screening method. However with the increasing availability of echocardiography including the advent of hand-held devices, echocardiography is now a routine investigation for patients with suspected cardiac disease even in the developing world. Indeed a significant number of patients are diagnosed with VHD incidentally

on trans-thoracic echocardiography performed for other reasons. In addition transthoracic echocardiography is an extremely valuable tool in the assessment of the severity of VHD. In the majority of patients, no other investigations are required but in selected cases other modalities such as trans-oesophageal echocardiography, cardiac magnetic resonance imaging and very occasionally cardiac catheterisation may be necessary to accurately assess severity.

1.2 SPECIFIC VALVE LESIONS

Different valvular lesions result in different pressure and volume loads within the heart and although ultimately if untreated they can all result in signs of cardiac failure, the pathophysiology of each valve lesion need to be considered carefully during the assessment. In addition the parameters measured on echocardiography and the guidelines for intervention vary considerably between lesions. A standardised approach to their assessment is therefore extremely important.

1.3 MITRAL STENOSIS

Mitral Stenosis (MS) remains a common valve lesion worldwide particularly in the developing countries. It remains a common problem in Auckland, New Zealand with the high immigrant population from the Pacific Islands. MS is almost always due to previous rheumatic fever but in a minority of cases can be congenital or due to very severe degenerative calcification of the mitral valve annulus that extends into the leaflets. Rheumatic MS results in thickening of the leaflets particularly at the tips

with fusion of the commissures. In addition there is thickening and shortening of the chordae. In more advanced cases there can be significant calcification. This results in decreased mobility of the leaflets both in systole and diastole with reduced valve opening. In addition the restriction of the leaflets can result in concomitant mitral regurgitation.

MS results in increased pressure loads within the left atrium, as blood needs to be forced through the reduced valve orifice. This results in left atrial dilatation, an increased pressure gradient across the mitral valve and the backpressure transmitted into the pulmonary circulation can lead to pulmonary congestion. In severe cases this can result in pulmonary hypertension and right ventricular failure. In contrast the left ventricle is not exposed to this increased pressure load and often LV-end diastolic pressures remain normal or even low.

1.3.1 CLINICAL ASSESSMENT

As above the presence or absence of symptoms is a vital part of the assessment of patients with MS. However it may be decades between the onset of rheumatic fever to the point at which symptoms develop. During this time many patients become more sedentary, often without realising it or attribute reduced exercise capacity down to the physiological effects of ageing so that the assessment to symptomatic status is not entirely straightforward. In addition careful assessment for signs of heart failure is important as well as determining the presence of atrial fibrillation (AF), which is a common finding in these patients. The combination of AF and MS is important to

recognise as they are at a much higher risk of thromboembolic complications that patients with non-valvular AF.

1.3.2 ECHOCARDIOGRAPHIC ASSESSMENT IN MITRAL STENOSIS

Rheumatic MS results in typical echocardiographic appearances on echocardiography (Figure 1.1). As above there is leaflet thickening, particularly at the tips. The restriction of motion in diastole results in a typical 'hockey stick' appearance in the parasternal long axis view.

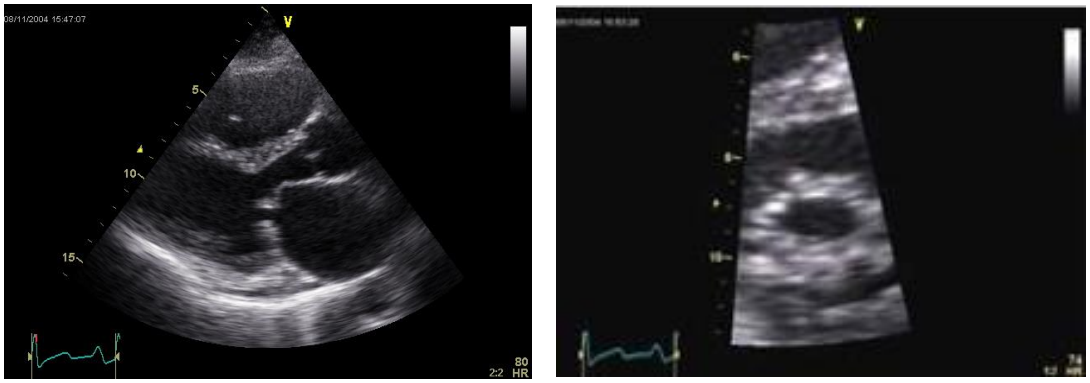


Fig 1.1 Parasternal long axis view (left) demonstrating a rheumatic mitral valve with typical 'hockey stick' appearance of the anterior mitral valve leaflet. Parasternal short axis view (right) shows thickening of leaflet tips with reduced valve opening.

The current guidelines for the assessment of the severity of mitral stenosis recommend the measurement of 3 key echocardiographic parameters on resting echocardiography [Baumgartner *et al* 2009]. These are the mitral valve area (MVA), the mean pressure gradient (MG) across the mitral valve and the pulmonary artery systolic pressure (PAP). This is in addition to standard echocardiography to assess chamber size, ventricular function and the assessment of other valves. However there are limitations with the assessment of all these parameters and it is not uncommon for different parameters to suggest different degrees of severity. There is also a problem of intra- and inter-observer variation and it is extremely important to minimise this variation when assessing severity over time.

There are 4 different methods of estimating MVA on echocardiography. These include planimetry of the valve using 2D or increasingly commonly 3D echocardiography, the pressure half-time method (PHT), the volumetric method and the proximal iso-velocity surface area (PISA) method. The 2 most commonly used methods on trans-thoracic echocardiography are planimetry and PHT.

The mean gradient is calculated by tracing around the velocity time integral obtained by tracing around the continuous wave Doppler signal through the mitral valve. The right ventricular systolic pressure is estimated from the maximum velocity of tricuspid regurgitation and added to an estimate of the right atrial pressure. In the absence of pulmonary stenosis this is approximately the same as the pulmonary artery pressure. However both of these parameters can be very heart rate dependant and coupled with the known difficulties in the methods of estimating mitral valve

area results in problems in accurately determining the overall severity of MS by resting echocardiography alone.

1.3.3 HAEMODYNAMIC CONSEQUENCES OF MITRAL STENOSIS

The main consequence of MS is a rise in the left atrial pressure in order to maintain left ventricular (LV) filling. Consequently the left ventricle is relatively protected against the increased pressure loads and consequently is relatively unaffected. However in severe cases of MS, overall LV ejection fraction may be reduced. This is usually as a result of increased calcification of the MV annulus resulting in decreased longitudinal motion and thickening and retraction of the chordal apparatus. The increased left atrial (LA) pressure results in significant LA dilatation. This predisposes to atrial fibrillation, which can further impair LV filling and is often poorly tolerated in MS. The high LA pressure is transmitted to the lungs leading to increased pulmonary pressure predisposing to signs and symptoms of heart failure include pulmonary oedema. Without intervention, MS progresses to the development of significant pulmonary hypertension and right ventricular (RV) dilatation and/or impairment of RV function. Consequently the aim of clinical and echocardiographic assessment is to identify patients with haemodynamically significant MS prior to the development of pulmonary hypertension or significant adverse remodelling.

1.3.4 RECOMMENDED INDICATIONS FOR VALVE INTERVENTION

Echocardiography performed at rest and the clinical assessment patients' symptoms are the cornerstones of established guidelines in determining the optimal timing of intervention. The American College of Cardiology/American Heart Association

(ACC/AHA) guidelines [Bonow *et al* 2006] in place during the period of this research for the timing of intervention in MS are summarised below (Figure 1.2).

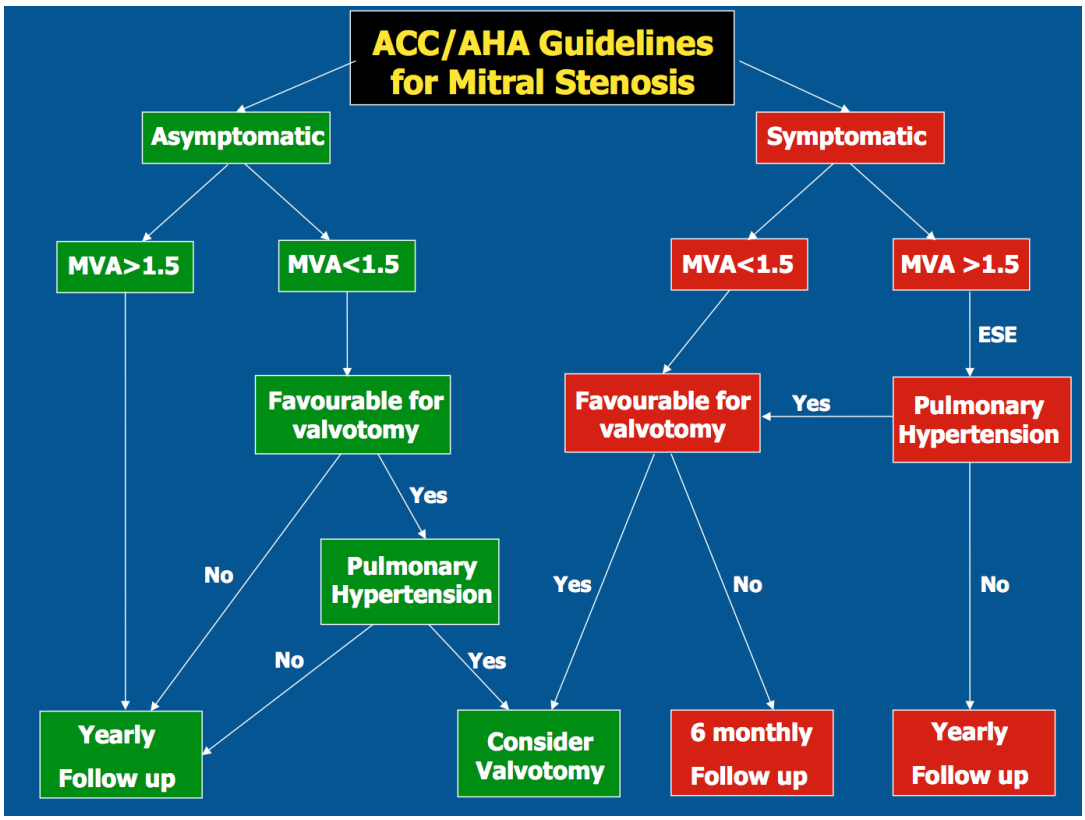


Figure 1.2. Criteria for intervention for Mitral Stenosis according to ACC/AHA criteria. [Bonow *et al* 2006]

In addition symptomatic patients with severe MS and pulmonary hypertension who are not suitable for percutaneous mitral balloon valvotomy (PMBV) should be considered for open commissurotomy or mitral valve replacement (class IIa)

According to these guidelines the key parameters in determining severity of disease in MS are mitral valve area, mean gradient across the mitral valve and pulmonary artery hypertension. The grading of severity of these parameters is listed in Table 1.1 [Baumgartner *et al* 2009]

Table 1.1 Criteria for assessing MS severity [Baumgartner *et al* 2009]

	Mild	Moderate	Severe
Specific Findings			
Mitral Valve Area (cm^2)	>1.5	1.0 – 1.5	<1.0
Supportive Findings			
Mean gradient (mmHg)	<5	5 - 10	>10
Pulmonary Artery Pressure (mmHg)	<30	30 - 50	>50

1.4 MITRAL REGURGITATION

Significant mitral regurgitation (MR) remains one of the commonest valve lesions encountered in clinical practice. Previous studies have found it to be the most common valve lesion in the United States of America [Nkomo *et al* 2006] and the second most common in Europe [Iung *et al* 2003]. Like MS it can remain asymptomatic for many years. The regurgitant flow into the LA during systole results in an increase volume and pressure load on the left atrium. However in the subsequent diastole, the left ventricle needs to accommodate this extra regurgitant volume in addition to the normal volume of blood that has passed through the pulmonary circulation. Therefore in contrast to MS, the left ventricle is exposed to wall stretch and in severe MR, significant LV dilation can occur. If valve surgery is delayed, this can result in irreversible impairment of LV function. Consequently the optimal timing of surgery in mitral regurgitation is crucial.

1.4.1 CAUSES OF MITRAL REGURGITATION

The fundamental cause of mitral regurgitation is a reduction in the normal coaptation of the anterior and posterior mitral valve leaflets [Enriquez-Sarano *et al* 2009]. There are a number of underlying mechanisms that can result in this loss of coaptation. Describing the mechanism of this failure of coaptation led to the classification system devised by Carpentier which is summarised in Table 1.2 [Carpentier 1983]. This is based on leaflet motion with Type 1 demonstrating normal leaflet motion, Type II displaying excessive motion and Type III resulting in restricted motion in systole (IIIa) or diastole (IIIb).

In western countries, the commonest causes of mitral regurgitation are degenerative, comprising myxomatous, flail leaflets, and annular calcification. These comprise around 60-70% of cases [Enriquez-Sarano *et al* 2009]. Ischaemic mitral regurgitation accounts for around 20% of cases with endocarditis and rheumatic accounting for around 2-5% each. However in New Zealand, particularly in the North Island there is a much larger proportion of patients presenting with rheumatic mitral regurgitation due to the large immigrant population from the Pacific Islands

Table 1.2. Causes of mitral regurgitation [Carpentier 1983, Enriquez-Sarano *et al* 2009]

	Organic		**Functional**	
	Type I	Type 2	Type IIIa	Type IIIb
Non-ischaemic	Endocarditis (perforation) Annular dilatation, Annular calcification Congenital (cleft)	Degenerative (flail/billowing) Endocarditis (ruptured chord) Traumatic (ruptured chord, PM)	Rheumatic, Iatrogenic (Radiation/Drugs) Inflammatory	Cardiomyopathy Myocarditis LV dysfunction
Ischaemic		Ruptured PM		Functional Ischaemic

PM : Papillary Muscle, LV : Left Ventricle

1.4.2 CLINICAL ASSESSMENT

The clinical assessment of patients with MR revolves around an accurate determination of the patient's symptomatic status and signs of heart failure or significant LV volume overload. However as with mitral stenosis, accurate determination of the point at which patients become symptomatic can be difficult and the physical signs of decompensation and LV volume overload occur late and should not be relied upon to determine the need for surgery [Bonow *et al* 2006]. Consequently echocardiographic assessment is crucial in determining the severity of mitral regurgitation and assessing for any significant haemodynamic consequences that may determine the need for surgery. The increased success of MV repair and the finding that patients with signs of early LV dysfunction or those with significantly dilated left ventricles do less favourably post MV surgery has also prompted the earlier referral of patients for consideration of MV repair.

1.4.3 ECHOCARDIOGRAPHIC ASSESSMENT

The key variables in assessing the severity of MR according to the European Association of Echocardiography/American Society of Echocardiography (EAE /ASE) recommendations are shown in Table 1.3. In addition assessment should be made of the haemodynamic consequences of MR including the measurement of chamber dimension or preferably chamber volumes and the estimation of pulmonary artery pressure.

Table 1.3 Guidelines for the assessment of native mitral regurgitation [Zoghbi *et al* 2003]

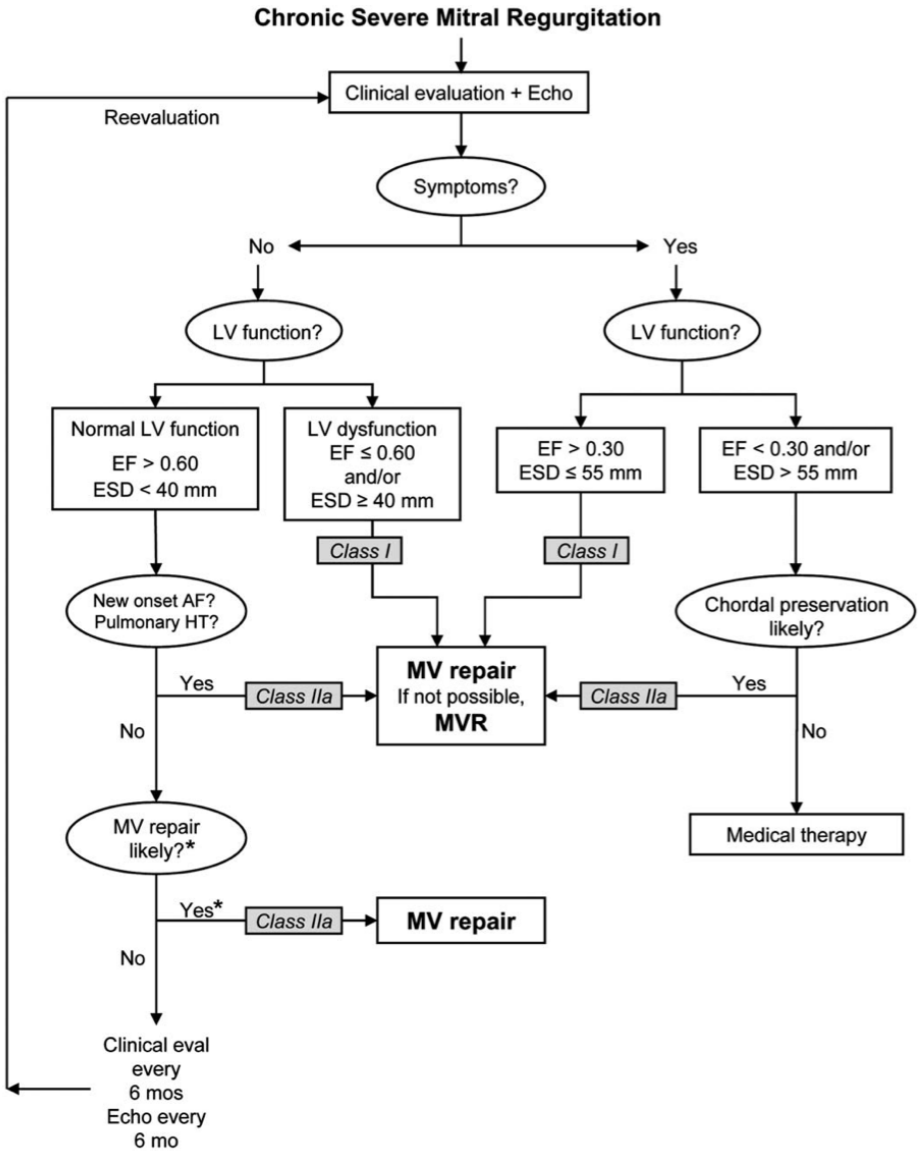
	Mild	**Moderate**		**Severe**
Specific Signs Of Severity				
Jet Size	Small central jet <4cm2 or <20% LA area	Signs of MR>mild present but no criteria for severe MR		>40% LA area or a wall impinging jet of any size swirling in LA
Vena Contracta	<0.3cm			>0.7cm for large central jet
Flow Convergence	None or minimal			Large flow convergence
Pulmonary Vein Flow	Systolic dominant flow			Systolic flow reversal
Leaflets				Prominent flail leaflet or ruptured papillary muscle
Supportive Signs				
Pulse Wave Doppler Mitral Valve	A-wave dominant inflow	Intermediate signs/findings		E-wave dominant inflow (E>1.2m/s)
Continuous Wave Doppler Density	Soft density, parabolic shape			Dense triangular signal
Left Atrial Size	Normal			Enlarged
Left Ventricular Size	Normal			Enlarged
Quantitative Parameters				
Regurgitant Volume (mls)	<30	30 – 44	45 – 59	
Regurgitant Fraction (%)	<30	30 – 39	40 – 49	≥60
Effective Regurgitant Orifice Area (cm^2)	<0.20	0.20 – 0.29	0.30 – 0.39	≥50

LA : left atrial; MR: Mitral regurgitation.

1.4.4 RECOMMENDATIONS FOR VALVE SURGERY

Symptomatic patients with severe MR have a class 1 indication for surgery regardless of LV size unless there is severe LV dysfunction. Similarly asymptomatic patients with Severe MR have a class 1 indication if there is very significant LV enlargement (end-systolic dimension >40mm) or signs of early LV dysfunction (LVEF <60%). The ACC/AHA recommendations for the management of chronic mitral regurgitation are summarised in Figure 1.3 [Bonow *et al* 2006]

However signs of haemodynamic compromise such as pulmonary hypertension or new onset atrial fibrillation should also prompt consideration of MV surgery (Class IIa). The presence of a prosthetic heart valve is associated with a complication rate of approximately 1% per year [Pibarot and Dumesnil 2009]. Consequently the benefits of surgery must outweigh not only the upfront risks of surgery but also the yearly risk of complications associated with a mechanical valve. Consequently MV replacement is not recommended in patients with severe MR if they are truly asymptomatic unless there are signs of haemodynamic compromise. Mitral valve repair is now much more successful with conversion to a MV replacement as low as 1% in high volume centres. Although the perioperative risks for an MV repair are similar and indeed often lower than that of a replacement, patients with a successful MV repair are not subject to the same annual rate of complications and lifelong anticoagulation is not required. Consequently provided local expertise in MV repair is available, referral for MV repair is recommended for all asymptomatic patients with severe MR if the chances of repair are high (Class IIa).



EF: Ejection Fraction, ESD: End-Systolic Diameter, MVR: Mitral Valve Replacement. MV: Mitral Valve, AF: Atrial Fibrillation, HT: Hypertension, LV: Left Ventricular

Figure 1.3 Recommendations for the management for chronic severe MR [Bonow *et al* 2006]

1.5 AORTIC STENOSIS

Aortic stenosis (AS) is the commonest valve lesion in Europe and with an ever-ageing population, the incidence of degenerative AS is likely to continue to rise. Of the different valve lesions, aortic stenosis has the most evidence to guide clinical practice. The recommendation to perform aortic valve replacement in symptomatic patients with severe AS is well established and has been shown to increase survival. However a number of difficulties remain, not least the management of patients with asymptomatic severe aortic stenosis and patients with low-flow, normal ejection fraction AS.

1.5.1 CAUSE OF AORTIC STENOSIS

The commonest causes of AS are calcific AS, bicuspid aortic valves, true congenital AS or AS secondary to rheumatic heart disease. Calcific aortic stenosis of either a tricuspid or bicuspid aortic valve is by far the most common. In calcific aortic stenosis it is believed that there is initial plaque formation in a similar manner to that of atherosclerosis. Indeed AS and significant atherosclerotic burden often co exist in the same patient. The on-going damage results in progressive calcification, which distorts blood flow through the valve orifice. This disruption in blood flow results in further areas of damage, thereby accelerating the calcific process. This disruption of flow is an important factor in the calcification that occurs in bicuspid valves which results in these patients presenting 1- 2 decades earlier than patients with tricuspid aortic valves.

1.5.2 CLINICAL ASSESSMENT

As with other valvular lesions, the presence of a typical murmur alerts the clinician to the possibility of underlying aortic stenosis and this may be found incidentally on physical examination. The presence of a softened second heart sound with the absence of an aortic component and a reduction in the upstroke of the carotid pulse is suggestive of severe aortic stenosis. However the presence or absence of these signs is an unreliable in determining the need for intervention or surgery. In addition, the accurate assessment of symptomatic status is extremely important as once patients with severe aortic stenosis become symptomatic, the survival without surgery is poor. Typical symptoms include exertional breathlessness or angina and in severe cases, syncope and sudden cardiac death.

1.5.3 ECHOCARDIOGRAPHIC ASSESSMENT

Echocardiography is the mainstay of diagnosis and assessment of severity. 2D echocardiography can identify the morphology of the aortic valve and in particular whether it is tricuspid. Visual assessment of the degree of leaflet excursion and the extent of thickening and calcification can be a good guide to overall severity. In addition the accurate assessment of left ventricular function and stroke volume is important to correctly interpret the findings from quantitative assessment of severity. The key parameters to quantify the severity of aortic stenosis are the aortic valve area (AVA), the mean pressure drop across the aortic valve and the peak velocity through the stenotic valve. Unlike for MS, planimetry using standard 2D transthoracic echocardiography is not recommended to calculate the AVA due to the difficulty in ensuring the ultrasound beam images is positioned at the leaflet tips. Furthermore

artefact from heavily calcified valves often precludes assessment. Consequently AVA is estimated using the continuity principle and based on the flow through the left ventricular outflow tract (LVOT) being equal to the flow through the aortic valve (in the absence of a left-to- right shunt through a ventricular septal defect). The peak velocity and mean gradient are derived from the continuous wave Doppler profile through the aortic valve. However it is essential that the maximum velocity is obtained and hence imaging from a number of different echocardiographic windows is necessary. The guidance for the assessment of AS severity is outlined in Table 1.4.

Table 1.4. Echocardiographic assessment for the severity of aortic stenosis

	Aortic sclerosis	**Mild Aortic Stenosis**	**Moderate Aortic Stenosis**	**Severe Aortic Stenosis**
Aortic Jet Velocity (m/s)	≤ 2.5	2.6–2.9	3.0–4.0	>4.0
Mean Gradient (mmHg)	-	<20 (<30[a])	20–40[b] (30–50[a])	>40[b] (>50[a])
AVA (cm^2)	-	>1.5	1.0 – 1.5	<1.0
Indexed AVA (cm^2/m^2)		>0.85	0.60 – 0.85	<0.6
Velocity Ratio		>0.50	025–0.50	<0.25

AVA : aortic valve area

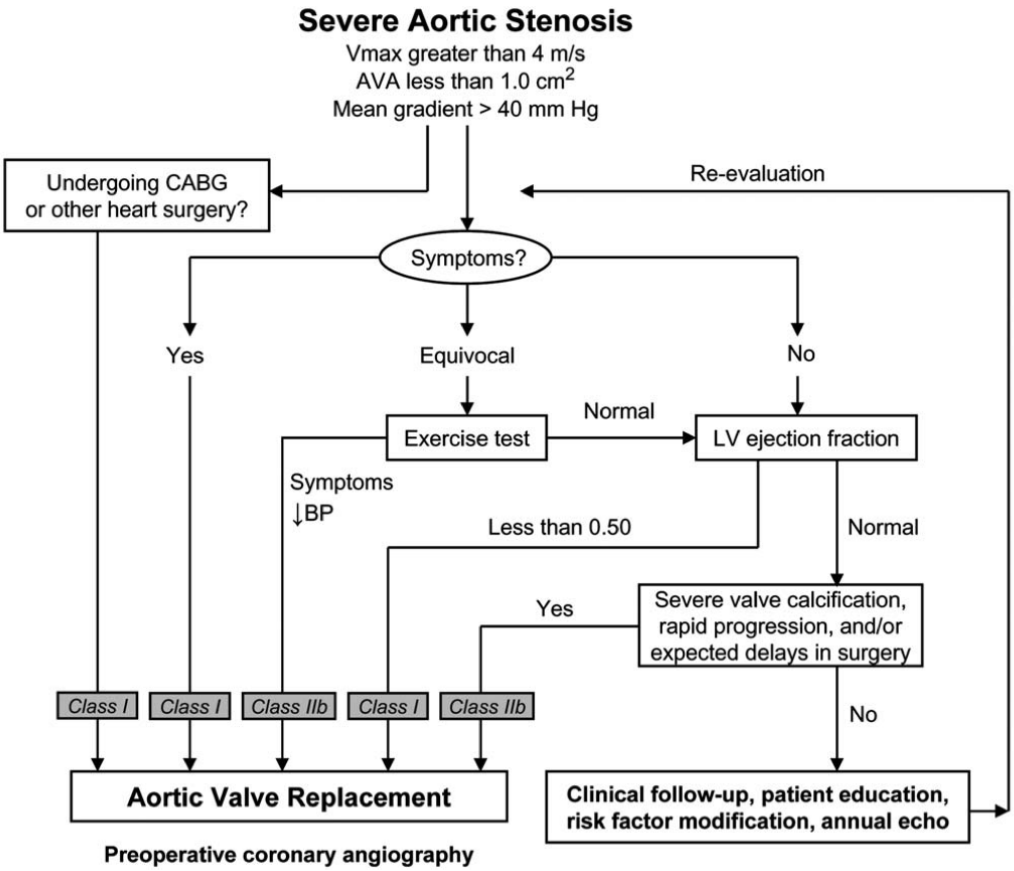
[a]ESC guidance [Vahanian *et al* 2007]

[b]ACC/AHA guidance [Bonow *et al* 2006]

1.5.4 GUIDELINES FOR INTERVENTION

There is clear consensus that operating on patients with symptomatic severe aortic stenosis is justified both to relive symptoms but to avoid the risk of sudden cardiac death. Severe aortic stenosis is defined as a peak velocity of >4m/s, a mean pressure drop of 40mm Hg and an AVA of <1.0cm^2 [Bonow *et al* 2006, Vahanian *et al* 2007]. The ACC/AHA guidelines for aortic valve replacement are summarised in Figure 1.4. Whilst these guidelines are universally accepted, there is a significant degree of variation regarding the valve area at which patients become symptomatic [Otto *et al* 1997]. This may result from variations in aortic compliance, body size, differential stroke volumes or an inability to accurately define the symptomatic status.

However the optimal management of asymptomatic patients with severe AS determined by resting echocardiographic parameters is uncertain. Asymptomatic patients with severe AS have a life expectancy similar to that of an age matched population without severe AS and their risk of sudden cardiac death is less than 1% per year [Pellikka *et al* 2005, Ross and Braunwald 1968]. This is lower that the surgical mortality of an aortic valve replacement (2-3%) and similar to the annual risk of complications of a prosthetic valve replacement [Pibarot and Dumesnil 2009]. Consequently routine aortic valve replacement (AVR) in all asymptomatic patients with severe AS will result in a higher cumulative risk to the AS population.



AVA: Aortic Valve Area, Vmax: Peak velocity through aortic valve, CABG: Coronary Artery Bypass Grafting, BP: Blood Pressure, LV: Left Ventricular

Figure 1.4. ACC/AHA guidelines for intervention in severe AS [Bonow *et al* 2006]

1.6 AORTIC REGURGITATION

1.6.1 CAUSES OF AORTIC REGURGITATION

The incidence of aortic regurgitation (AR) is less well defined that that of other valvular lesions. Singh et al described an incidence of around 13% in men and 8.5% of women but when stratified by age, less than 1% of patients had greater than moderate AR except in those over 70 years of age [Singh *et al* 1999].

There are a number of causes of AR that include abnormalities of the valve or dilatation of the aorta. Common causes of chronic AR are listed in table 1.5. In developed countries, bicuspid aortic valves and abnormalities of the aortic root are the most common cause of AR. However worldwide and in particularly in developing countries, AR secondary to rheumatic fever remains common.

Table 1.5 Causes of Aortic Regurgitation

Valve causes
Bicuspid aortic Valve
Previous endocarditis
Degenerative valve disease
Rheumatic fever
Aortic causes
Dilatation of the aortic root
Marfan's disease
Hypertension
Connective tissue disease
Aortic dissection
Syphilis

1.6.2 CLINICAL ASSESSMENT

Acute severe AR especially in the context of aortic dissection is a surgical emergency and rapid diagnosis by clinical assessment, echocardiography and if appropriate computed tomography is vital. In contrast however chronic AR can remain clinically stable for many years. Chronic AR results in an increased volume load on the left ventricle and consequently patients can develop significant LV chamber dilatation. Ultimately this progresses to LV dysfunction and the development of symptoms such as dyspnea, decreased exercise capacity or pulmonary congestion.

The typical clinical signs include an early diastolic murmur, systolic hypertension and a wide pulse pressure. In addition the increased forward flow through the aortic valve causes a systolic flow murmur. The elevated systolic pressure and large stroke volume result in a number of eponymous clinical signs including a bounding carotid pulse (Corrigan's pulse), head bobbing (de Musset's sign), pulsation of he uvula (Muller's sign), and pistol shot sounds over the femoral artery with compression (Traube's sign). During compression with a glass slide, capillary pulsations (Quincke's sign) can be seen on the fingernail [Bekeredjian and Grayburn 2005]. In addition in severe AR significant LV dilatation can result in a displaced, hyper-dynamic apex beat.

1.6.3 ECHOCARDIOGRAPHIC ASSESSMENT

Echocardiography is the most important diagnostic test in AR. It allows assessment of valve morphology, including whether there is a bicuspid or tricuspid valve. In addition assessment of the aortic root size can be made and if there is significant dilatation of the aortic root this may prompt consideration of aortic root and valve replacement even if the AR is not severe. Quantitative and qualitative assessment of AR severity can also be performed. The key parameters to assess AR severity are similar to those in MR and include assessment of the vena contracta width, the effective orifice area calculated via the PISA method and the regurgitant volume calculated by the PISA method or the continuity method. In addition other parameters include the ratio of the LVOT to AR jet width, the AR jet area to the LVOT area and the pressure half time of AR. Other supporting features of moderate

to severe AR include flow reversal in the descending thoracic and abdominal aorta respectively. However many of these measurements can be more difficult to perform in AR than in MR. Indeed of all valve lesions, echocardiographic assessment of severity in AR is arguably the most difficult to perform precisely and other modalities such as trans-oesophageal echocardiography, cardiac magnetic resonance imaging and cardiac catheterisation can be helpful. The echocardiographic criteria for the assessment of AR are shown in Table 1.6

Other key parameters to assess on echocardiography are signs of early left ventricular dysfunction or increasing chamber dilatation. Indeed if excessive chamber dilation occurs and/or LV function becomes depressed, this may not normalize after AVR. Furthermore patients, who are symptomatic, have decreased LV function (LVEF <50%) or severe LV dilatation (LV end systolic dimension: 50–55 mm) have a poorer outcome after AVR [Bonow *et al* 2006, Gabriel *et al* 2008, Vahanian *et al* 2007].

Table1.6. Guidelines for the assessment of severity of native aortic regurgitation [Zoghbi *et al* 2003]

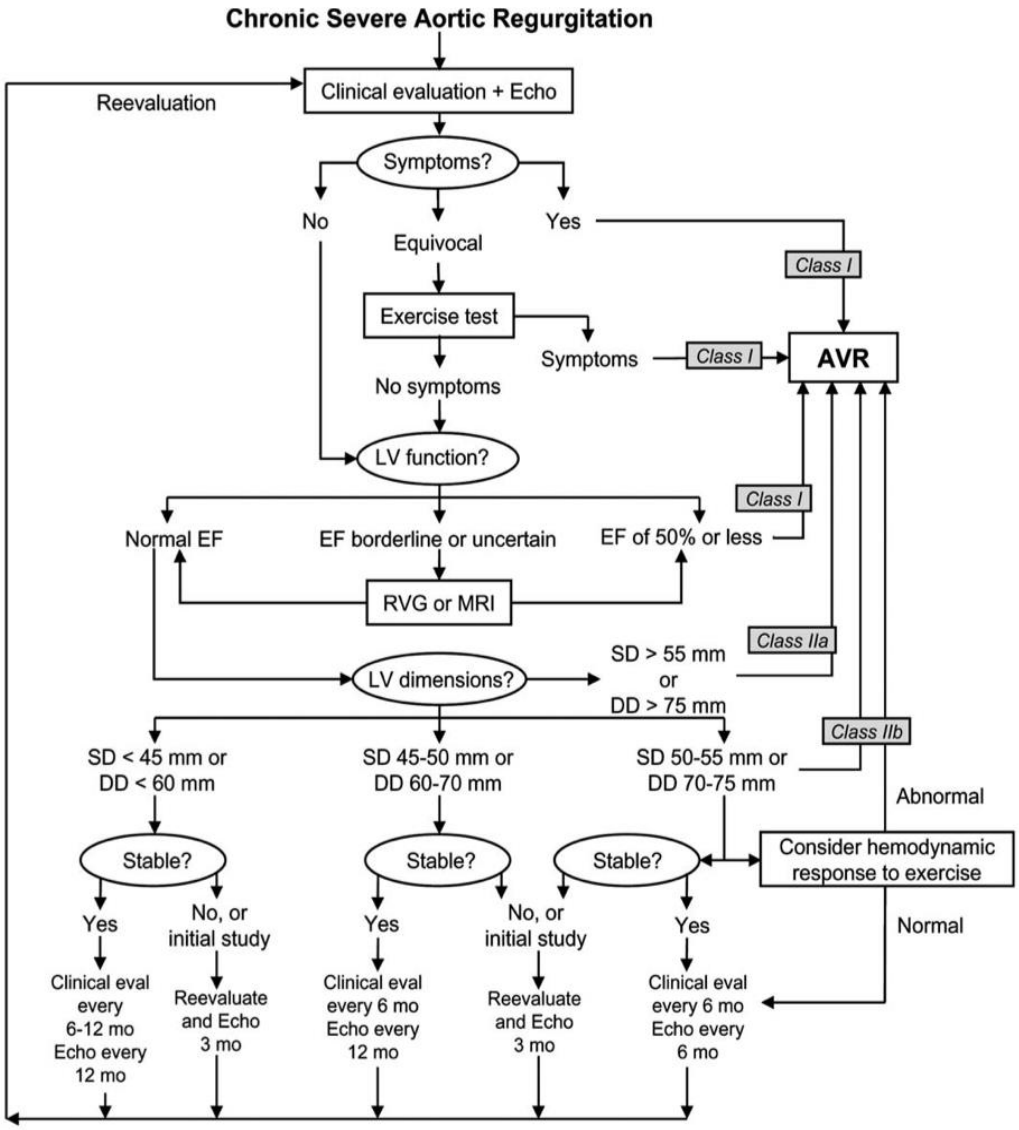
	Mild	**Moderate**		**Severe**
Structural Parameters				
Left Atrial Size	Normal	Normal or dilated		Usually dilated
Aortic Leaflets	Normal or abnormal	Normal or abnormal		Abnormal or flail / wide coaptation defect
Doppler Variables				
Jet Width In LVOT	Small	Intermediate		Large in centre jets; variable in eccentric jets
Jet Density	Incomplete or faint	Dense		Dense
Pressure Half Time (ms)	Slow >500	Medium 500 – 200		Steep <200
Diastolic Flow Reversal In DA	Brief early diastolic reversal	Intermediate		Prominent holodiastolic reversal
Quantitative Variables				
Vena Contracta Width (cm)	<0.3	0.30 – 0.60		>0.6
Jet Width/LVOT Width (%)	<25	25 – 45	46 – 64	≥65
Jet Area/LVOT Area (%)	<5	5 – 20	21 – 59	≥60
Regurgitant Volume (mls)	<30	30 – 44	45 – 59	≥60
Regurgitant Fraction (%)	<30	30 – 39	40 – 49	≥50
Effective Regurgitant Orifice Area (cm^2)	<0.10	0.10 – 0.19	0.20 – 0.29	≥0.30

LVOT: Left ventricular outflow Tract; DA: Descending aorta

1.6.4 GUIDELINES FOR CONSIDERATION OF VALVE INTERVENTION IN AR

The decision to intervene in chronic severe AR is based on the patient's symptomatic status and the degree of LV dilatation or dysfunction if the patient remains asymptomatic. These guidelines are summarized in Figure 1.5. Current criteria for LV dilatation include an end-systolic dimension of greater than 55mm or an end diastolic diameter of 75mm. In addition LV dysfunction is defined as an ejection fraction of less than 50%.

If there is difficulty determining the symptomatic status, exercise testing can be considered. However it remains unclear what constitutes an abnormal exercise test and what parameters should be assessed in AR. In addition other modalities such as Cardiac magnetic resonance imaging can be very helpful in assessing the severity of MR by calculating the regurgitant volume and assessing LV volumes. However again it remains unclear what cut-offs should be used to determine referral for cardiac surgery. As with other valve disease this is vitally important as the death rate for asymptomatic patients with normal LV size and function is extremely low at <0.2% per year [Dujardin *et al* 1999].



AVR: Aortic Valve Replacement, MRI: Magnetic Resonance Imaging, RVG: Radionuclide Ventriculography, SD: End-systolic Dimension, DD: End-diastolic Dimension, EF: ejection fraction, LV: Left Ventricular

Figure 1.5 Guidelines for the management of severe Chronic AR [Bonow *et al* 2006]

1.7 THE NEED FOR ALTERNATIVE METHODS FOR THE ASSESSMENT OF VHD

The role of echocardiography performed at rest is well established in the assessment of the severity of valvular heart disease. Similarly there is reasonable evidence that valve surgery or intervention in symptomatic patients with severe valve disease is appropriate to improve symptomatic status and improve prognosis. Consequently this is a class 1 indication for surgery in most guidelines for the management of VHD provided the operative risks are acceptable.

However there are number of difficulties in clinical practice with this approach. Firstly as discussed the onset of symptoms can be extremely difficult to assess accurately on clinical assessment alone. This is vitally important, as longitudinal studies have shown that whilst the prognosis of asymptomatic patients with severe valve disease is good, even mild symptoms are associated with a much poorer prognosis [Klodas *et al* 1997, Ross and Braunwald 1968]. With an ageing population and a more sedentary lifestyle, the accurate assessment of symptomatic status is becoming more difficult.

Secondly a number of patients may be symptomatic despite seemingly mild or moderate disease as assessed on echocardiography performed at rest. These patients may have evidence of haemodynamically significant valve disease detected on exercise stress echocardiography and this can be associated with a poorer prognosis if untreated [Magne *et al* 2010].

Thirdly patients with severe VHD may develop significant LV dilatation and possibly early LV dysfunction or pulmonary hypertension without becoming symptomatic [Vahanian *et al* 2007]. These patients remain at risk of other cardiovascular complications such as the onset of atrial fibrillation and a small excess risk of sudden cardiac death. In addition their operative mortality in the presence of LV dysfunction of pulmonary hypertension is increased and there is a reduced probability of LV size and function returning to normal post surgical repair.

Finally the echocardiographic assessment of valve disease severity can be difficult and without careful, detailed protocols and good quality assurance within departments, inter-observer and intra-observer variability can be a significant issue. In addition in more complex cases, the need for further specialist investigations combined with the need for regular follow-up places a large strain on echocardiography departments and financial resources. This is a major problem in developing countries where there is a high burden of VHD.

To overcome these difficulties, previous research has focussed on 2 key areas to better risk stratify asymptomatic patients with severe VHD or those patients whose symptoms are out of keeping with the severity of VHD on resting echocardiography. These are the role of exercise stress echocardiography and the measurement of plasma natriuretic peptide concentrations.

1.8 STRESS ECHOCARDIOGRAPHY IN VHD

Stress echocardiography has a number of potential benefits in assessing patients with valvular heart disease. Low-dose dobutamine stress echocardiography has an established role in patients with severe aortic stenosis who have a reduced LV ejection fraction. This allow differentiation between true severe aortic stenosis and pseudo-aortic stenosis in which reduced valve opening is due to low stroke volumes in the context of LV impairment rather than valve stenosis. In addition it allows the assessment of contractile reserve in patients with poor LV ejection fraction to assess their suitability to undergo major cardiac surgery. Stress echocardiography with dobutamine can also be used to assess for co-existing myocardial ischaemia that may be contributing to the patients symptoms or look for worsening of ischaemic mitral regurgitation. There is also limited data in using dobutamine stress echocardiography in the assessment to mitral stenosis [Reis *et al* 2004]

Physiological stress in the form of treadmill exercise or a cycle ergometer is generally more helpful in the assessment of valvular heart disease. The 2006 guidelines (Bonow et al. 2006) on the management of VHD formally recommended exercise stress echocardiography/electrocardiography for asymptomatic patients with severe AS (peak velocity >4m/s or mean gradient >40mmHg) and in asymptomatic moderate or severe MS (MVA <1.5cm2). They also suggested exercise testing may be helpful in symptomatic patients with mild MS. For patients with MS, a rise in PAP of >60mm Hg or a pulmonary capillary wedge pressure (PCWP) of >25mm Hg was considered an indication for intervention. In patients with AR and MR there was

no clear recommendation made about when to consider exercise testing. These recommendations are predominantly consensus driven and it is unclear whether this approach is helpful in clinical practice.

However performing exercise testing on patients with VHD provides an objective measure of functional capacity and overcomes many of the difficulties in assessing this based on clinical assessment alone. Furthermore exercise stress echocardiography has the ability to identify haemodynamic consequences of severe VHD such as pulmonary hypertension with exercise, a failure to augment systolic blood pressure or reduced contractile reserve. Abnormalities on exercise testing may suggest that the underlying VHD is more severe than indicated by resting echocardiography alone and prompt the clinician to reassess the severity of VHD or consider the need for valve surgery.

1.9 NATRIURETIC PEPTIDES IN VALVULAR HEART DISEASE

1.9.1 WHAT ARE NATRIURETIC PEPTIDES

The vasoactive properties of atrial tissue were first identified in 1981 when it was demonstrated that infusion of extracted atrial tissue caused significant diuresis in rats [Agnoletti *et al* 1987]. Following on from this observation a number of peptides have been identified with significant diuretic and natriuretic properties. These peptides form an important role in regulation of blood pressure and the maintenance of plasma

volume. There are 3 natriuretic peptides, atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide [Levin *et al* 1998].

As the name suggests, atrial natriuretic peptide (ANP) is released predominantly by the atria. This is mainly in response to an increase in atrial wall stretch. Brain natriuretic peptide (BNP) was originally identified in extracts of porcine brain. Although it is also contained within the human brain, much higher quantities are found within the ventricles of the heart. Brain natriuretic peptide release is more closely related to ventricular wall stretch [Qi *et al* 2001, Yoshimura *et al* 1993]. C-type natriuretic peptide is predominantly found within the central nervous system, anterior pituitary and kidney. Very low levels of C-type natriuretic peptide are found in plasma making it of less use in clinical practice. Both ANP and BNP are derived from pro hormones that are cleaved into an inactive N terminal component (NT pro-BNP, NT pro-ANP) and the active peptide. The N-terminal fragments are more stable in vivo and hence often used as surrogates for the active component. However direct measurement of the active component has theoretical advantages when looking to identify significant changes in natriuretic peptide concentrations over a short time period.

1.9.2 THE CARDIOVASCULAR EFFECTS OF NATRIURETIC PEPTIDES

The cardiovascular effects of natriuretic peptides are complex and act through a variety of mechanisms to reduce blood pressure and intravascular circulating volume. The main mechanisms of action are considered below:

1.9.3 NATRIURESIS

Natriuretic peptide (NPs) acts directly on the kidney to produce both natriuresis and diuresis. NPs cause dilatation of the afferent renal arterioles leading to an increase in blood flow and greater filtration of plasma [Marin-Grez *et al* 1986]. They cause relaxation of mesangial cells, which creates a greater surface area for filtration [Fried *et al* 1986, Stockand and Sansom 1997]. In addition NPs act directly on the tubules to promote natriuresis [Schulz-Knappe *et al* 1988].

1.9.4 INHIBITION OF THE RENIN ANGIOTENSIN ALDOSTERONE SYSTEM

Natriuretic peptides inhibit sodium and water reuptake within the proximal convoluted tubules [Harris *et al* 1987]. Within the collecting ducts they act through the inhibition of vasopressin and via cyclic guanosine monophosphate (cGMP) to further inhibit water and sodium reabsorption [Dillingham and Anderson 1986, Light *et al* 1989, Sonnenberg *et al* 1986, Zeidel 1995, Zeidel *et al* 1988].

1.9.5 EXTRAVASCULAR FLUID SHIFT

Natriuretic peptides reduce the circulating volume by causing a shift of fluid from the intravascular to the extravascular space. This is through an increase in permeability of vascular endothelial cells and an increase in hydrostatic pressure within the capillary bed [Levin *et al* 1998].

1.9.6 EFFECTS ON THE SYMPATHETIC NERVOUS SYSTEM

Natriuretic peptides reduce sympathetic tone predominantly by suppression of the sympathetic outflow from the central nervous system (Figure 1.6). In addition they inhibit the vagal activation in response to a lowering of circulating volume thereby suppressing the reflex vasoconstriction and relative tachycardia that would normally occur.

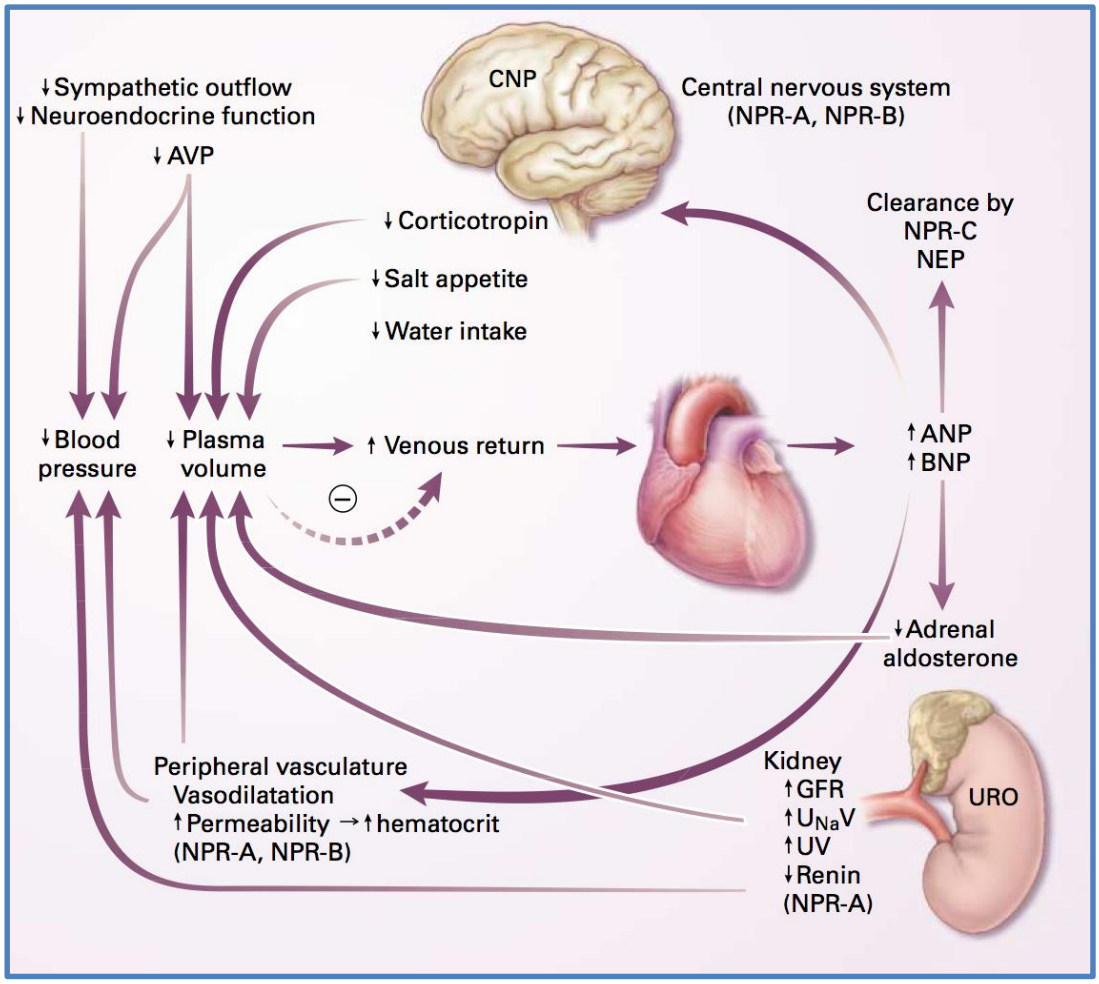


Figure 1.6 Physiological effects of natriuretic peptides [Levin *et al* 1998]

1.9.7 PATHOPHYSIOLOGY OF NATRIURETIC PEPTIDES

As outlined above the release of natriuretic peptides is closely linked to atrial (predominantly ANP) and ventricular (predominantly BNP) wall stretch. Consequently conditions that result in an increasing wall stretch of the cardiac chambers result in increased circulating levels of natriuretic peptides. In particular congestive cardiac failure results in very high plasma concentrations of natriuretic peptides and consequently BNP in particular has been studied extensively in heart failure. Indeed measurement of BNP or NT-Pro BNP is recommended in contemporary guidelines for the investigation of patients with dyspnoea [Dickstein *et al* 2008]. These guidelines suggest that low plasma concentrations of BNP in a patient presenting with dyspnoea make it extremely unlikely that heart failure is the cause of their symptoms. Plasma BNP concentrations have also been used to monitor response to heart failure treatment with a failure of BNP levels to fall with treatment associated with an adverse prognosis. It has also been suggested that plasma concentrations of natriuretic peptides may become elevated before the onset of symptoms in patients with left ventricular systolic dysfunction and that they increase progressively with the severity of left ventricular impairment [McDonagh *et al* 1998, Qi *et al* 2001].

Brain natriuretic peptide concentrations measured early after myocardial infarction are a strong predictor of mortality, even after adjusting for left ventricular ejection fraction [de Lemos *et al* 2001, Omland *et al* 1996, Richards *et al* 1999]. Experimental animal models suggest that increased BNP may be a marker of the transition from compensated to overt heart failure [Langenickel *et al* 2000]. However

published data on changes in natriuretic peptides in valvular heart disease are more limited [Gerber *et al* 2003, Gerber *et al* 2003, Prasad *et al* 1997, Qi *et al* 2001].

1.9.8 THE POTENTIAL ROLE OF NATRIURETIC PEPTIDES IN VALVULAR HEART DISEASE

Natriuretic peptides have the potential to be extremely useful in the assessment of patients with VHD who do not have an established indication for surgery. They are easily measurably with a number of well-established assays [Yandle *et al* 1993]. Due to their pathophysiology, plasma levels are increased with left ventricular wall stretch and consequently they may offer complementary information to that of echocardiography in VHD. Elevation of plasma natriuretic peptides concentrations may predate the onset of symptoms in patients with cardiac failure and given the known difficulty in symptomatic assessment, measurement of natriuretic peptide concentrations may be extremely helpful in VHD. Like in congestive cardiac failure, VHD results in increased volume and pressure loads on the cardiac chambers. However in VHD the cardiac chambers that are exposed to these increased haemodynamic loads vary significantly depending on the type of valve lesion. For example in mitral stenosis, the left atrium is exposed to significant pressure overload and ultimately high degrees of wall stretch as the chamber dilates. However the left ventricle in this setting is not exposed to increased pressure or volume overload and is in fact often relatively small and under-filled. Conversely in aortic regurgitation, the left ventricle is exposed to a large volume and dilates with consequently increasing wall stretch but the left atrium is relatively protected from increased pressure or volume overload until left ventricular dysfunction develops.

Understanding the response to natriuretic peptides in different valve lesions is therefore essential in determining whether they can be useful in the management of patients with heart valve disease.

Furthermore defining the exact onset of symptoms can be challenging and accurate assessment is vital to ensure that patients are not exposed to risks of sudden cardiac death and cardiac failure if not appropriately referred for surgery. It has been shown that natriuretic peptide levels in symptomatic patients are higher in than asymptomatic patients [Gerber *et al* 2003] and again this may provide further information regarding the haemodynamic consequences of the underlying valve lesion. However it remains unclear whether NPs can accurately identify patients with severe VHD and what degree of elevation of plasma concentration should prompt further assessment.

In addition although exercise stress echocardiography (SE) has an important role in assessing symptomatic status and the haemodynamic response to exercise in VHD, SE does not feature prominently in clinical guidelines and when it is recommended it is done so predominantly on the basis of expert opinion. It remains unclear which parameters should be assessed on SE and what adverse features predict the need for intervention.

1.9.8 GENERAL HYPOTHESIS

1. Given that VHD results in wall stretch of either the atria or the ventricles, it is hypothesised that either atrial natriuretic peptide and/or brain type natriuretic peptides may be useful in detecting patients with haemodynamically significant valve disease or those with an adverse prognosis.

2. That stress echocardiography may perform better in identifying patients with haemodynamically significant VHD or those with an adverse prognosis than clinical assessment and resting echocardiography alone.

1.10 AIMS OF THIS STUDY

The aims of thesis were to

In VHD patients without an indication for valve surgery (Chapter 3)

- Assess the role of exercise stress echocardiography in VHD
- Determine whether exercise stress echocardiography can identify patients at high risk of adverse events

In patients with mitral stenosis (Chapter 4)

- Compare and contrast the ability of BNP and ANP to identify patients with haemodynamically significant VHD.

In patients with mitral regurgitation (Chapter 5)

- To determine whether BNP can identify patients with signs of early LV dysfunction either at rest or with exercise

In patients with aortic regurgitation (Chapter 6)

- To determine whether BNP can identify patients with signs of early LV dysfunction either at rest or with exercise

In patients with VHD (Chapter 7)

- To compare and contrast the level of BNP across different valvular lesions
- To determine whether BNP can identify patients with more severe valve disease irrespective of underlying valve lesion.

CHAPTER TWO:

METHODS

2.1 INTRODUCTION

Valvular heart lesions lead to abnormal cardiovascular physiology and an increase in either intra-cardiac pressure or an increased volume load within the heart. Moreover different valvular lesions result in different degrees of pressure and volume overload. Due to the fact that in chronic valve disease these pressure and volume loads increase gradually over time, it can be difficult to define the when intervention should be considered. The point at which to intervene depends on a number of different factors. This includes the extent to which the underlying valve lesion is impacting the patient's lifestyle and indeed the patient's symptomatic status features heavily in established guidelines for the management of VHD [Bonow *et al* 2006]. Other factors to consider are the underlying severity of valve disease as assessed by echocardiography, the reparability of the valve defect and the risk of future complications. However as discussed there are a number of difficulties with this approach in clinical practice and stress echocardiography and/or measurement of natriuretic peptides may help to identify patients who would benefit from intervention at an early stage.

2.1.1 STRESS ECHOCARDIOGRAPHY

Exercise stress echocardiography has been used for the assessment of possible underlying ischaemic heart disease for many years. However it is gaining an increasing role in the assessment of valvular heat disease and its use does feature in established guidelines for VHD [Bonow *et al* 2006]. However it remains unclear what variables to measure and whether the use of exercise stress echocardiography

alters clinical outcome. In addition newer echocardiographic techniques such as the assessment of contractile reserve, tissue Doppler imaging and either Doppler or speckle-tracking derived strain and strain rate measurements may better identify patients with haemodynamically significant valve disease compared to standard assessment alone.

2.1.2 NATRIURETIC PEPTIDES

Natriuretic peptides are known to increase in conditions that result in increased wall stretch within the heart. They have an established use in the assessment of patients with suspected cardiac failure. They have been shown to exclude heart failure in patients with dyspnoea if concentrations remain within the normal range [Dickstein *et al* 2008]. In addition elevated plasma concentrations have been associated with adverse prognosis in a number of conditions such as myocardial infarction [Omland *et al* 1996], heart failure [Anand *et al* 2003] and pulmonary embolism [Coutance *et al* 2008]. However little is known about their ability to identify patients with significant valve disease.

2.2 GENERAL METHODOLOGY

2.2.1 STUDY DESIGN

We undertook a case-control study comparing patients with different valvular lesions and age and sex matched controls. All patients underwent comprehensive clinical assessment; resting echocardiography and sampling of plasma natriuretic peptides

immediately prior to exercise stress echocardiography. Natriuretic peptides were also measured immediately post exercise. Patients underwent follow up for a period of 2 years after enrollment.

2.2.2 STUDY POPULATION

Patients with isolated valve lesions of at least moderate severity were identified from the outpatient clinics or echocardiograms reports conducted at Middlemore hospital, Otahuhu, New Zealand or Green Lane Cardiovascular Unit, Auckland City Hospital, New Zealand. Age and sex matched controls were recruited by advertisement.

2.2.3 INCLUSION CRITERIA

1. At least moderate valve disease defined as follows:
    a. Moderate to severe aortic stenosis (peak velocity >3m/s)
    b. Moderate to severe aortic regurgitation (AR:LVOT ratio >0.3)
    c. Moderate to severe mitral stenosis (MVA<1.5cm^2)
    d. Moderate-severe or severe mitral regurgitation (EROA>0.3cm$^{2)}$
2. Normal LV systolic function (aortic stenosis EF>50%, aortic regurgitation EF>50%, mitral regurgitation EF>60% and mitral stenosis EF>50%).
3. Aged 18 and able to give informed consent

2.2.4 EXCLUSION CRITERIA

The exclusion criteria included known ischaemic heart disease, significant renal impairment (creatinine >160 µmol/L, respiratory disease, and an inability to walk on

a treadmill or a contraindication to exercise testing. Patients with any other valvular lesion other than the inclusion valve lesion graded more than mild in severity were excluded from the study.

2.2.5 ETHICAL APPROVAL

The study was approved by the Auckland Regional Ethics Committee. All patients gave informed written consent prior to inclusion in the study.

2.3 CLINICAL ASSESSMENT

All patients underwent comprehensive assessment by an experienced cardiologist at the time of enrollment. This included documentation of any co-existing medical conditions, relevant cardiovascular medications and assessment for any pre specified exclusion criteria. The case report form is attached in Appendix 1. The patients symptomatic status was assessed according to the New York Heart Association (NYHA) criteria by the cardiologist blinded to the result of the echocardiographic, exercise treadmill data and peptide levels.

2.4 ECHOCARDIOGRAPHY

2.4.1 STANDARD ECHOCARDIOGRAPHY

All echocardiograms were performed by experienced sonographers on modern commercially available echo machines (Vivid 7, General Electric Vingmed

Ultrasound, Norway). All patients underwent comprehensive examination including M-mode, 2D, Doppler and tissue Doppler echocardiography modified according to their underlying valvular lesions consistent with current guidelines [Baumgartner *et al* 2009, Zoghbi *et al* 2003]. Sample study protocols are shown in Appendix 2 and 3.

2.4.2 ANALYSIS OF CHAMBER VOLUMES

The LV end-systolic and end-diastolic volumes and LV ejection fraction were measured from the apical four-chamber view using the modified Simpson's single-plane method [Leung *et al* 1996]. This method was chosen to allow comparison with the post-exercise volumes. The left atrial area was measured in the apical four-chamber view [Lester *et al* 1999]. The right ventricular dimension and fractional area change were measure in the apical 4-chamber view. LV mass was calculated from linear dimensions using the American Society of Echocardiography recommended formula [Lang *et al* 2005].

2.4.3 ASSESSMENT OF AORTIC STENOSIS SEVERITY

Quantitative and qualitative measures of aortic stenosis severity were made according to American Society of Echocardiography guidelines [Baumgartner *et al* 2009]. Quantitative measures of AS severity included peak velocity, mean pressure drop and aortic valve area.

Measurement Of Aortic Peak Velocity And Mean Gradient

The view with the highest recorded velocity was used to obtain the maximum aortic velocity. The mean gradient was obtained from tracing around this Doppler profile. All measurements were averaged over 3-5 beats.

Calculation Of Aortic Valve Area

The continuity principle was utilised to estimate the aortic valve area. The flow of blood through the LVOT was calculated by placing a pulse wave Doppler (PW) sample in the LVOT in the apical 5 chamber view and tracing around the signal to calculate the velocity time integral (VTI) and multiplying by the LVOT area. The LVOT was assumed to be circular and hence the LVOT area was calculated by the formula:

$$\text{LVOT area} = \pi * (\text{LVOT diameter}/2)^2$$

The VTI through the aortic valve was calculated by tracing around a continuous wave Doppler (CW) signal through the aortic valve in the apical 5-chamber view. In the absence of a left to right shunt, the flow through the LVOT and through the aortic valve is equal.

$$VTI_{LVOT} * Area_{LVOT} = VTI_{AV} * AVA$$

Therefore we calculated the AVA according to the formula

$$AVA = (VTI_{LVOT} * Area_{LVOT}) \ / \ VTI_{AV}$$

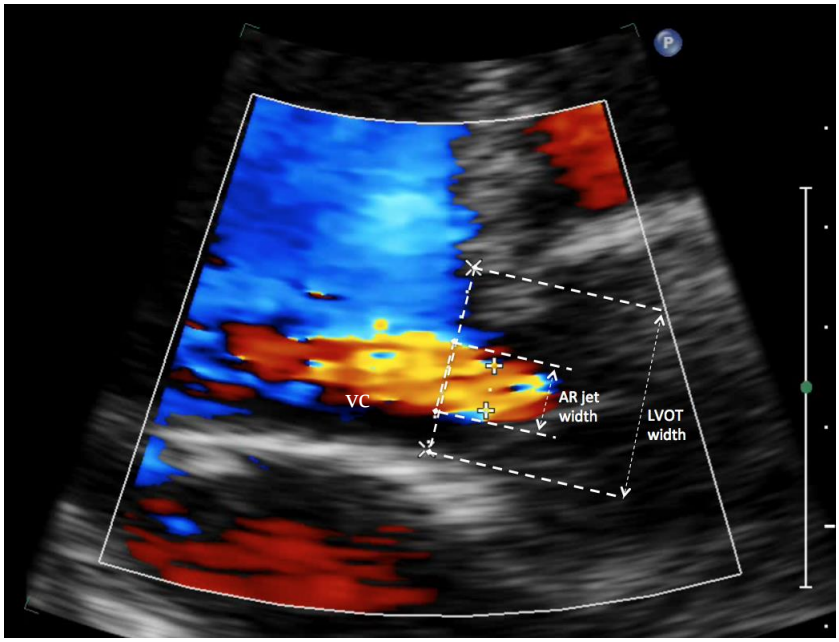
2.4.4 ASSESSMENT OF AR SEVERITY

Quantitative and qualitative measures of aortic regurgitation severity were made according to American Society of Echocardiography guidelines [Zoghbi *et al* 2003]. Quantitative measures included AR jet:LVOT width ratio, vena contracta, effective regurgitant orifice area, regurgitant volume, AR pressure half time and peak diastolic and end-diastolic flow velocities in the descending thoracic and abdominal aorta. Regurgitant volume was calculated via the continuity and PISA methods.

Measurement Of LVOT:AR Jet Width Ratio And Vena Contracta

This was obtained from a zoomed image of the LVOT. The jet width was measured at the same place as the LVOT dimension. The vena contracta was measured just distal to the area of flow convergence at the narrowest point. (Figure 2.1)

Figure 2 .1 Measurement of LVOT: AR jet ratio and Vena Contracta



LVOT: Left Ventricular Outflow Tract, AR: Aortic Regurgitation, VC : Vena Contracta

Quantification Of AR

The effective orifice area was calculated using the proximal isovelocity surface area (PISA) as described above. The AR radius was measured in either a zoomed parasternal long axis (PLAX) view or the apical 5-chamber view. The Nyquist limit was reduced to allow better delineation of the area of flow convergence. The peak AR velocity was measured from a CW Doppler profile measured from the apical 5-chamber view. The VTI signal was traced from the apical 5-chamber view to allow calculation of the regurgitant volume.

In addition the regurgitant volume was calculated using the volumetric method. The mitral valve inflow was calculated by multiplying the mitral annular cross sectional area by the VTI obtained from a PW sample placed at the level of the mitral valve annulus. The mitral annular area was estimated from the mitral annular diameter and

assuming a circular orifice. The LVOT flow was calculated as previously described by obtaining the VTI from a PW sample placed in the LVOT and multiplying by the cross sectional area of the LVOT. The regurgitant volume was obtained by subtracting the MV inflow form the LVOT forward flow.

The peak and end diastolic velocities from the diastolic flow reversal within the descending aorta were obtained from a PW sample placed in the proximal descending aorta.

2.4.5 ASSESSMENT OF MR SEVERITY

The severity of MR was assessed according to established guidelines [Zoghbi *et al* 2003]. MR severity was assessed semi-quantitatively using the vena contracta and measurement of the jet area.

The effective orifice area was calculated using the PISA and continuity methods [Enriquez-Sarano *et al* 1995]. The radius of flow convergence was measured in the apical 4-chamber view. The Nyquist limit was reduced to approximately 40cm/s to facilitate clearer definition of the area of flow convergence. The peak velocity of the MR jet was obtained from a CW signal in the apical 4-chamber view. The regurgitant volume was calculated by tracing around the MR VTI signal.

For the volumetric method the LVOT flow was calculated from the PW VTI signal and LVOT area as described above. The mitral valve inflow was calculated from the PW VTI signal obtained from the MV annulus and multiplied by the area of the MV

annulus. The regurgitant volume was calculated by subtracting the LVOT outflow from the MV inflow.

The stroke volumes obtained from the two methods were averaged to give a mean regurgitant volume. [Detaint *et al* 2005]

2.4.6 ASSESSMENT OF MS SEVERITY

The mitral valve area (MVA) was obtained using direct planimetry, pressure half time, proximal isovelocity area and continuity methods as described below [Hatle *et al* 1978, Martin *et al* 1979, Nakatani *et al* 1988]. The median MVA from these four methods was used for analysis.

Planimetry Assessment Of MV Area

This was performed in the parasternal short axis view. The ultrasound beam was scanned through the valve until it imaged the tips of the valve. The image was frozen the area of valve opening estimated by tracing around it in mid diastole. The main limitation of this method is that due to the conical shape of the mitral valve opening, positioning of the beam only a few millimetres towards the LA side of the valve can result in significant overestimation of the MVA.

Pressure Half Time Method

This method of calculating mitral valve area was first described in 1978 [Hatle *et al* 1979]. It is based on the concept that the rate of decline of a pressure gradient across the mitral valve orifice is determined partly by the size of the orifice, although other

factors such as the degree of left atrial and left ventricular compliance and the LV end diastolic pressure also affect this. The early (E) trans-mitral Doppler signal typically has triangular shape with a steady rate of decline from the maximum to the baseline. The PHT is defined as the time in milliseconds for the trans-mitral diastolic pressure gradient to fall from any value to half that value but in clinical practice it is the time from the maximum velocity to half the maximum value (Figure 2.2)

A CW sample was placed through the MV in the apical 4-chamber view. The sweep speed and scale were optimised to maximise the size of the CW profile on the screen. A line was drawn from the maximum velocity along the profile of the CW jet to calculate the pressure half time, The mitral valve area was estimated from the formula :

Mitral valve orifice area = 220/PHT

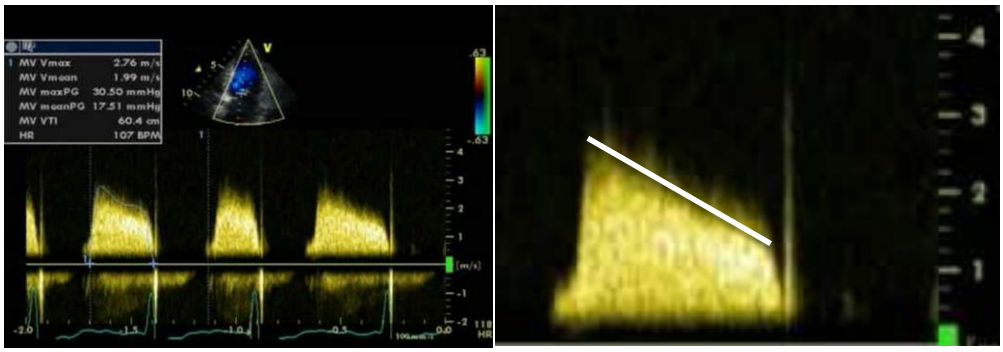


Figure 2.2 Calculation of Mitral valve are using the Pressure half time method

Continuity Method

This is a common method utilised across different valve lesions to assess the severity. In the case of MS it is based that in the absence of a shunt or coexisting regurgitant lesions, the flow through the mitral valve orifice in diastole should be the

same as the flow through the LVOT in systole. The flow of blood through the LVOT was calculated as described above by placing a PW sample in the LVOT and tracing around the signal to calculate the velocity time integral (VTI) and multiplying by the LVOT area. The LVOT was assumed to be circular and hence the LVOT area was calculated by the formula:

$$\text{LVOT area} = \pi * (\text{LVOT diameter}/2)^2$$

In the absence of any significant shunts or regurgitation, the outflow though the LVOT should be equal to the inflow through the mitral valve.

$$VTI_{LVOT} * Area_{LVOT} = VTI_{MV} * MVA$$

Therefore the MVA was calculated according to the formula:

$$MVA = (VTI_{LVOT} * Area_{LVOT}) / VTI_{MV}$$

Proximal Iso-velocity Area Method

This is also based on the continuity principle and assumes that the flow through the MW on the LA side must be equal to the flow through the valve emerging on the LV side. It does not require the assessment of flow through the aortic valve. As blood converges from the LA towards a narrowed mitral valve orifice, the velocity must increase to allow the blood to flow through the valve orifice. At any given distance from the orifice, the velocity of blood will be equal, resulting in a series of

hemispherical arcs radiating out from the orifice. By using the concept of aliasing, the velocity at which the Doppler colour scale changes from positive to negative, the Nyquist limit (NL) the velocity at one of these arcs can be determined. Consequently by using the surface area of a hemisphere ($2\pi r^2$) and the velocity of blood flow, the flow through the mitral valve can be calculated using the following formula

$$\text{Flow through MV} = 2\pi r^2 * \text{NL}$$

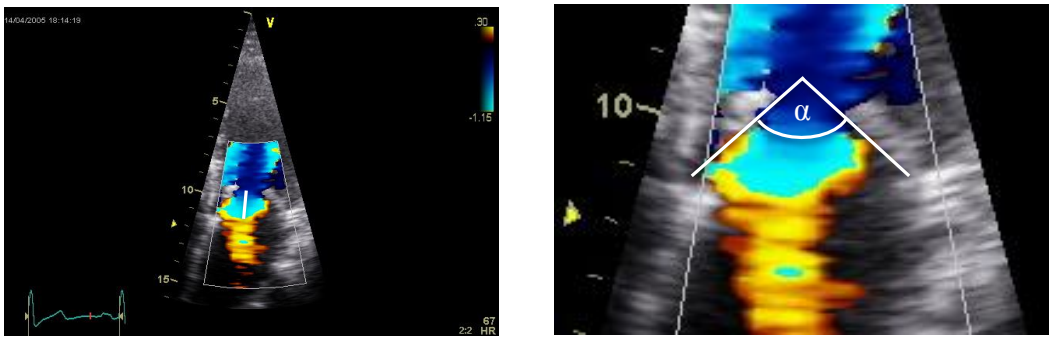


Figure 2.3. Flow convergence on the LA side of the mitral valve. The PISA radius is measured from the point of aliasing to the mitral valve orifice. Due to the area of flow convergence becoming constrained due to the mitral valve leaflets, only a portion of a hemisphere of flow convergence is present. It is therefore necessary to modify the calculation by multiplying by the angle α/180.

The Nyquist Limit (NL) was set at approximately 40cm/s to minimise measurement error of the PISA radius. However unlike in MR, whereby the regurgitant orifice, is relatively perpendicular to the velocity of blood allowing the formation of a complete hemisphere (except in eccentric jets), in MS the hemisphere is constrained by the angle (α) of the valve leaflets (Figure 2.3). Consequently significantly less than a full

hemisphere is obtained and hence an angle correction must be performed to use this in MS.

$$\text{Flow through MV in MS} = 2\pi r^2 * NL * (\alpha/180)$$

$$(\alpha/180) * 2\pi r^2 * NL = MVA * MV_{vmax}$$

$$\text{Consequently } MVA = (2\pi r^2 * \alpha/180 * NL) / MV_{vmax.}$$

Mitral Valve Area Used For Calculation

The median MVA obtained from these methods was used for analysis.

Mean Trans-mitral Pressure Gradient

Mean trans-mitral pressure gradients were obtained by tracing the continuous wave Doppler signal across the mitral valve [Quinones *et al* 2002].

2.4.7 MEASUREMENT OF PULMONARY ARTERIAL PRESSURE

To facilitate estimation of right ventricular (RV) systolic pressure, agitated saline was injected to enhance the tricuspid regurgitation profile [Himelman *et al* 1989]. The peak pulmonary artery systolic pressure (PAP) was derived using the simplified Bernouilli equation from the peak tricuspid regurgitant jet and added to an estimate of right atrial pressure obtained from imaging of the inferior vena cava [Otto 2000].

2.4.8 INDEXING TO BODY SURFACE AREA

Left atrial area, left ventricular volumes, valve areas and effective regurgitant orifice areas were indexed to body surface area [DuBois and DuBois 1916]

2.4.9 ASSESSMENT OF DIASTOLIC FUNCTION

Diastolic function was assessed using measurements of trans-mitral early (E) and late (A) inflow velocities at the mitral valve leaflet tips using a 5 mm sample volume in the apical four- chamber window. Pulsed wave tissue Doppler imaging of the mitral annulus was taken by placing a 5 mm sample volume at the junction of the LV wall and the septal and lateral mitral valve annulus. Care was taken to ensure the smallest possible angle between the ultrasound beam and longitudinal myocardial motion. The septal E/E' ratio was used to give an estimate of LV filling pressure.

2.4.10 ECHOCARDIOGRAPHY POST EXERCISE

Echocardiographic images were obtained immediately following peak exercise. Apical four-chamber views were obtained first for LV volumes and then after injection of agitated saline for the TR profile to estimate pulmonary artery pressure. In most patients images were obtained in less than 1-minute post exercise.

2.4.11 SPECKLE TRACKING DERIVED STRAIN

In the aortic regurgitation cohort, additional images were obtained pre and post exercise for 2D speckle tracking based LV longitudinal strain, strain rate and torsion measurements. However LV torsion measurements could not be reliably obtained

after exercise.

2.4.12 ECHOCARDIOGRAPHIC ANALYSIS

Images were stored digitally and analysis was performed offline (Echopac PC version 4.0.0 GE Healthcare, Milwaukee, WI, USA) by an experienced cardiologist blinded to the results of the patient characteristics and peptide data. All measurements were averaged from averaged from three to five cardiac cycles.

2.4.13 QUALITY ASSURANCE

All echocardiograms were performed and interpreted by experienced operators in a nationally recognised echocardiography department. Formal quality assurance programmes where in place and reviewed regularly within the department. A limited number of observers performed the echocardiograms or performed the analysis. The main criteria used for the assessment of valve severity have been shown to be highly reproducible. In aortic stenosis, Doppler estimates of aortic valve area, and mean gradient in aortic stenosis have been shown to have the intra-observer variability and reproducibility coefficients have been previously shown to be 1.88% and 0.16 m/s for V_{max}, 2.05% and 0.18 cm^2 for aortic valve area and 7.87% and 6.30 mmHg for mean gradient. For inter-observer variability, the variation and reproducibility coefficients were 2.00% and 0.14 m/s for V_{max}, 7.67% and 0.16 cm^2 for AVA and 8.53% and 7.06 mmHg for mean gradient respectively. Both intra- and inter-observer studies showed excellent intraclass correlation coefficients (ICC) for all echocardiographic parameters (ICC ranged from 0.943 to 0.992) [Moura *et al* 2011].

In mitral stenosis both inter and observer agreement for the assessment of MVA non invasively found it to be highly reproducible with good inter-observer agreement (ICC was 0.95 and 0.90 for PHT) and intra-observer agreement (ICC was 0.92 and 0.96) [Zamorano *et al* 2004]

In this study, the measurement of LV volumes, which have a greater degree of variation than other measures, were performed by a single operator.

2.5 EXERCISE TESTING

2.5.1 PROTOCOL

All patients underwent symptom-limited exercise testing on a motorized treadmill (GE/Marquette T2000, GE Healthcare, Milwaukee, WI, USA). A standard Bruce protocol was used for patients with mitral regurgitation. However it was noted that there was significant clustering of exercise times at the end of each stage and this was felt to adversely affect the objectivity of the determination of exercise capacity. Consequently for subsequent patients, the protocol was adjusted so that the speed and/or incline of the treadmill were increased at 1-minute intervals. The maximum workload at the end of each 3-minute stage remained equivalent to that of the standard Bruce protocol. The exercise protocol is attached in appendix 6.

2.5.2 PATIENT MONITORING

All patients underwent continuous ECG monitoring throughout the test. Blood pressure (BP) was recorded by an automated blood pressure cuff (SunTech Tango+,

SunTech Medical, Morrisville, NC, USA) placed on the left arm. BP was recorded at 1 minute then 2 minute intervals.

2.5.3 TERMINATION CRITERIA

Exercise was stopped for significant dyspnoea, chest discomfort, presyncope, fatigue or at patient request.

2.6 MEASUREMENT OF NATRIURETIC PEPTIDES

Blood samples were obtained from an indwelling intravenous catheter after 15 min lying supine, immediately prior to the baseline echocardiogram and immediately post exercise. Patients fasted for 2 hours prior to the investigations. Blood samples were collected in ethylene diamine tetraacetic acid tubes (7.5 mg/5 mL; Vacutainer, Becton Dickinson, Rutherford, NI). They were centrifuged for 10 minutes at 4°C and plasma stored at –80 °C. The samples were sent to the Department of Endocrinology at the Christchurch Heart Institute for measurement of natriuretic peptides at the completion of the study.

2.6.1 EXTRACTION OF ANP AND BNP FROM PLASMA

BNP and ANP were extracted from human plasma on reverse phase cartridges and the extract subjected to established radioimmunoassays [Yandle *et al* 1993]. For measurement of BNP concentrations, plasma was extracted on 500 mg SepPak vac C18 reverse phase cartridges, washed and eluted with 80% isopropanol in 0.1% Trifluroacetic acid (TFA). The extract is dried under air and reconstituted in assay

buffer. The antiserum used was hBNP-32 antiserum (Cat # RAS9086, Peninsula Laboratories, USA), raised in rabbit. [^{125}I]BNP-32 prepared by ChloramineT iodination and purified by high performance liquid chromatography (HPLC) was used as a tracer.

For measurement of ANP concentrations, 3mL of plasma was extracted on 500 mg SepPak vac C18 reverse phase cartridges, washed and eluted with 80% isopropanol in 0.1% TFA. The extract is dried under air and reconstituted in assay buffer. Locally raised hANP (99-126) (R31) raised in a rabbit was used as antiserum. [^{125}I]hANP (99-126) prepared by Chloramine T iodination and purified by HPLC.

2.6.2 ASSAY CHARACTERISTICS

The upper limit of the normal reference range for BNP is 42 pg/mL. The intra-assay coefficients of variation were 10.11 % at 25.7 pg/mL and 6.79% at 52.5 pg/mL and 13.76% at 82.4 pg/mL. The inter-assay coefficients of variation were 15.02% at 25.7 pg/mL and 15.74% at 52.5 pg/mL and 14.88% at 82.4 pg/mL.

The upper limit of the normal reference range for ANP is 83pg/mL. The intra-assay coefficients of variation were 5.82% at 50.8 pg/mL and 5.66% at 80.2 pg/mL and 5.68% at 247.2 pg/mL. The inter-assay coefficients of variation were 8.47% at 50.8 pg/mL and 13.05% at 80.2 pg/mL and 5.1% at 247.2 pg/mL

To convert BNP levels expressed in pg/mL to pmol/L, divide by 3.47 ad for ANP divide by 3.08 [Van Pelt *et al* 2007, Yandle *et al* 1993].

2.7 STATISTICAL ANALYSIS

Categorical data were presented as frequency and percentage, and continuous data were presented as mean ± standard deviation (SD), or median and inter-quartile range (IQR). BNP underwent natural log transformation in analyses due to its right skewed distributions unless specified, and was reported as median and inter-quartile range. Two sample student t-tests or Mann Whitney U test (for non-normally distributed data) were used for comparing continuous variables between patient groups. Comparison of all valves versus the control group, and comparison of valve subgroups was performed using the Chi-square or Fisher's exact tests for categorical data where appropriate. For comparison between subgroup of valves, one-way analysis of variance (ANOVA) was performed followed by the Dunnett's test, was used to compare each valve with control subjects. The Kruskal-Wallis test was used when the continuous data was not normally distributed. Pearson correlation coefficients or Spearman correlation coefficients were reported for linear associations. SAS released 8.0 software (SAS Institute Inc., Cary, NL, USA) and R 2.1.1(The R Foundation for Statistical Computing) was used for analysis. All tests were two tailed and a p-value of <0.05 was considered statistically significant.

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CHAPTER THREE

EXERCISE STRESS ECHOCARDIOGRAPHY IN VALVULAR HEART DISEASE

Sharma V, Newby DE, Stewart RAH *et al*
Exercise echocardiography in patients with valvular heart disease
(Echo Research and Practice - 2015;2(3):89-98.

3.1 SUMMARY

Stress echocardiography is recommended for the assessment of asymptomatic patients with severe valvular heart disease (VHD) when there is discrepancy between symptoms and resting markers of severity. The aim of this study was to determine the prognostic value of exercise stress echocardiography in patients with common valve lesions.

One hundred and fifteen patients with VHD (AS n=28; AR n=35; MR n=26; MS n=26), and age- and sex-matched controls (n=39) with normal ejection fraction underwent exercise stress echocardiography. The primary end point was a composite of death or hospitalisation for heart failure.

Asymptomatic VHD patients had lower exercise capacity than controls and 37% of patients achieved less than 85% of their predicted metabolic equivalents (METs). There were 3 deaths, 4 hospital admissions and 24 patients underwent surgery during follow-up. An abnormal stress echocardiogram (METs <5, blood pressure rise <20 mm Hg, or PAP post exercise >60 mmHg) was associated with an increased risk of death or hospital admission (12% vs 2%, p=0.03). The assessment of contractile reserve did not offer additional predictive value.

An abnormal stress echocardiogram is associated with an increased rate of death and hospitalisation with heart failure at 2 years. Stress echocardiography should be considered as part of the routine follow up of all asymptomatic patients with VHD.

3.2 INTRODUCTION

Valvular heart disease (VHD) remains a common cause of cardiovascular morbidity and mortality worldwide. Acute valvular lesions such as acute aortic or mitral regurgitation often present with signs of acute severe heart failure and the prognosis without urgent cardiac surgery is poor. In contrast patients with chronic valve disease may remain asymptomatic for many years. Previous studies have demonstrated that during this asymptomatic phase, the prognosis remains relatively favourable but once symptoms develop, the prognosis without valve surgery becomes poor [Delahaye *et al* 1991, Horstkotte and Loogen 1988, Klodas *et al* 1997, Ross and Braunwald 1968, Wood 1954]. Consequently the assessment of symptomatic status in patients with VHD forms a key factor in current guidelines on the management of VHD [Bonow et al 2006, Nishimura et al 2014]. However due to the often slowly progressive nature of VHD, defining the exact onset of symptoms in patients with VHD can be difficult. In addition many patients who remain asymptomatic can develop significant dilatation of cardiac chambers and impairment of ventricular function or pulmonary hypertension prior to developing overt symptoms. In many patients, the assessment of the severity of the underlying valve disease can be problematic with discordant markers of severity on resting echocardiography. Furthermore a number of patients complain of symptoms despite objectively mild or moderate valve disease at rest.

3.2.1 RECOMMENDATIONS FOR STRESS ECHOCARDIOGRAPHY IN VHD

To overcome these difficulties current guidelines [Bonow et al 2006, Nishimura et al 2014] recommend the use of exercise testing in patients with valve disease.

However this is mainly consensus driven and it is unclear whether performing exercise echocardiography in VHD patients leads to a clinical for these patients.

3.2.2 STUDY AIMS

The aim of this study was to determine the value of performing exercise echocardiography in patients with common valvular heart lesions without an established indication for surgery according to current guidelines. We aim to determine whether patients who demonstrate adverse features on stress echocardiography have a worse outcome during follow up than those with normal exercise stress echocardiograms. A secondary aim was to compare the value of exercise stress echocardiography across different valve lesions.

3.3 METHODS

3.3.1 PATIENT SELECTION

Asymptomatic patients with severe valve disease, patients with a discrepancy between symptoms and Doppler echocardiography performed at rest or those with equivocal symptoms were identified from echocardiogram reports and outpatient clinics in the Auckland region. These comprised patients with isolated aortic stenosis, aortic regurgitation, mitral regurgitation and mitral stenosis. All patients had normal left ventricular ejection fraction (AS ≥ 50%, AR >50%, MR ≥ 60%, MS≥ 50) [Baumgartner *et al* 2009, Bonow *et al* 2006, Zoghbi *et al* 2003]. Exclusion criteria

included ischaemic heart disease, significant renal impairment (creatinine >160 μmol/L), respiratory disease, a contraindication to exercise testing, additional valvular lesions graded greater than mild or an established indication for valve surgery according to the ACC/AHA guideline criteria [Bonow *et al* 2006, Nishimura *et al* 2008]. All patients eligible for inclusion were invited to participate. The patients' symptomatic status was assessed according to the NYHA criteria by an experienced cardiologist blinded to echocardiographic data. Control subjects were volunteers from the local community who were age and sex matched. They were recruited by advertisement and had no clinical evidence of cardiovascular or respiratory disease. The study was approved by the Northern X Ethics Committee, Auckland. All patients gave written consent after a full explanation of the purpose and nature of all procedures used.

3.3.2 ECHOCARDIOGRAPHY

All patients underwent comprehensive echocardiography at rest as outlined in section 2. All analysis was performed offline by an experienced cardiologist blinded to the results of the patients' clinical assessment. All measurements were averaged from at least 3, or in cases of AF, 5 cardiac cycles.

Quantitative and qualitative measures of aortic stenosis and regurgitation severity were made according to American Society of Echocardiography guidelines [Baumgartner *et al* 2009, Zoghbi *et al* 2003]. Quantitative measures of AS severity included peak velocity, mean pressure drop and aortic valve area. Assessment of AR

severity included the AR jet:LVOT width ratio, AR pressure half time, peak diastolic and end-diastolic flow velocities in the descending thoracic and abdominal aorta.

The severity of MR was assessed by quantitative Doppler with mitral and aortic stroke volumes [Enriquez-Sarano *et al* 1993] and by the PISA method [Enriquez-Sarano *et al* 1995]. The stroke volumes obtained from the two methods were averaged to give a mean regurgitant volume [Detaint *et al* 2005]. The mitral valve area was obtained using direct planimetry, pressure half time, and continuity methods [Hatle *et al* 1978, Martin *et al* 1979, Nakatani *et al* 1988]. The median MVA from these three methods was used for analysis. Mean trans-mitral pressure gradients were obtained by tracing the continuous wave Doppler signal across the mitral valve [Quinones *et al* 2002].

3.3.3 ESTIMATION OF PULMONARY ARTERY PRESSURE

To facilitate estimation of RV systolic pressure, agitated saline was injected to enhance the tricuspid regurgitation profile as described in Section 2 [Himelman *et al* 1989]. The peak PAP was derived using the simplified Bernouilli equation from the peak tricuspid regurgitant jet velocity and added to an estimate of right atrial pressure obtained from imaging of the inferior vena cava [Otto 2000].

3.3.4 INDEXING TO BODY SURFACE AREA

Left atrial area, left ventricular volumes, valve areas and effective regurgitant orifice areas were indexed to body surface area [DuBois and DuBois 1916].

3.3.5 EXERCISE STRESS ECHOCARDIOGRAPHY

All patients underwent symptom-limited exercise testing on a motorized treadmill. A standard Bruce protocol was used for patients with MR. However it was noted that there was significant clustering of exercise times at the end of each stage and this was felt to adversely affect the objectivity of the determination of exercise capacity. Consequently for subsequent patients, the protocol was adjusted so that the speed and/or incline of the treadmill were increased at 1-min intervals. The maximum workload at the end of each 3-min stage remained equivalent to that of the standard Bruce protocol. Exercise was stopped for significant dyspnoea, chest discomfort, presyncope, fatigue or at patient request.

Immediately after exercise echocardiographic images were obtained in the apical four-chamber view, first for LV volumes then for tricuspid regurgitant jet velocity with agitated saline enhancement. In all patients, data were obtained within 1 min of peak exercise.

3.3.6 OUTCOME MEASURES

Patients continued with their regular clinical follow up by their usual cardiologist in accordance with established guidelines [Bonow *et al* 2006]. Their clinical cardiologist decided the requirement for, and timing of any valve intervention blinded to exercise echo data. The only exception to this was if there were major abnormalities detected on stress echocardiography in which case the cardiologist was informed. Follow up data was collected for two years from the date of enrolment. The main outcomes were death, hospitalisation for heart failure and the need for

valve replacement surgery. The primary clinical outcome was a composite of death and hospitalisation for acute heart failure. The secondary endpoint was a composite of death, hospitalisation and valve intervention.

Adverse features on treadmill testing were defined as low exercise capacity (<5 metabolic equivalents (METs) on treadmill exercise [Fletcher *et al* 1995, McCully *et al* 2002], an abnormal blood pressure response to exercise (<20 mmHg rise with exercise) [Bonow *et al* 2006], exercise induced pulmonary hypertension (PAP >60 mmHg post exercise [Bonow *et al* 2006]) and poor contractile reserve (<4% increase in ejection fraction post exercise) [Lee *et al* 2005, Marechaux *et al* 2008].

3.3.7 STATISTICAL ANALYSIS

Two sample student t-tests were used for comparing continuous variables between patient groups. Comparison of all valves versus the control group, and valve sub-groups was performed using the Chi-square or Fisher's exact tests for categorical data where appropriate. For continuous variables, two independent sample Student's t-test was used for comparing all valves versus controls group. For comparison between subgroup of valves, one-way analysis of variance (ANOVA) was performed. Chi squared test was used for categorical variables. Prediction accuracies were reported by area under the receiver operating characteristic curve (AUC) and its 95% confidence interval. Kaplan Meier curves were used to visualize the time to first clinical event across different stress echocardiographic parameters. XLSTAT (Version 2014.4.06, Addinsoft 1995-2014) was used for analysis. All tests were two tailed and a p-value of <0.05 was considered statistically significant.

3.4 RESULTS

All patients who agreed to participate completed all aspects of the study. One hundred and fifteen patients with valve disease and 39 control subjects were recruited: isolated MR (n=26), AR (n=35), AS (n=28) and MS (n=26) or normal valves (n=39) (Table 3.1)

Eighty-one (70%) of VHD patients were assessed as asymptomatic (NYHA class 1). The remainder had mild or equivocal symptoms but did not fulfil criteria for surgery based on their assessment of valve severity according to Doppler echocardiography and clinical assessment performed at rest. Across all VHD patients, 37 (32%) of patients had severe valve disease, 69 (60%) of patients had moderate valve disease and 9 (8%) of patients had mild disease but had symptoms out of keeping with their echocardiographic findings at rest. No patients had evidence of regional wall motion abnormalities at rest or immediately post exercise.

Table 3.1 Clinical characteristics and exercise echocardiogram data

	Controls (n=39)	Normal ESE (n=64)	Abnormal ESE (n=51)	P value (normal ESE vs controls)	P value (abnormal vs normal ESE)
Baseline Characteristics					
Mitral Regurgitation n (%)		16 (25)	10 (20)		0.49
Mitral Stenosis n (%)		4 (6)	22 (43)		<0.0001
Aortic Stenosis n (%)		10 (16)	18 (35)		0.01
Aortic Regurgitation n (%)		34 (53)	1 (2)		<0.0001
Age (years)	55±15	48±14	58±15	0.02	<0.0001
Body Mass Index (kg/m^2)	26±4	28±4	29±5	0.01	0.46
Sex Male (n,%)	23 (59)	50 (78)	23 (45)	0.06	<0.001
NYHA Class 2 (n, %)	0 (0)	11 (17)	23 (45)	0.07	0.001
Resting Echocardiography					
Left Atrial Area Index (cm^2/m^2)	11±2	12±4	16±6	0.01	< 0.0001
LVEDV (mls/m^2)	52±13	77±28	54±19	< 0.0001	< 0.0001
LVESVI (mls/m^2)	19±7	57±30	39±18	< 0.0001	< 0.0001
Left Ventricular EF (%)	64 (8)	64±6	63±8	0.71	0.38
Pulmonary Artery Pressure (mmHg)	24±4	29±6	37±13	< 0.0001	< 0.0001
Exercise Stress Echocardiography					
LVEDVI (mls/m^2)	34±13	57±20	40±18	< 0.0001	< 0.0001
LVESVI (mls/m^2)	9±5	17±9	12±7	< 0.0001	0.004
Left Ventricular EF (%)	78±8	71±8	71±10	< 0.0001	0.87
Change In Ejection Fraction (%)	13±7	7±8	7±16	0.001	0.79
Pulmonary Artery Pressure (mmHg)	41±9	46±8	64±20	0.02	< 0.0001
Metabolic Equivalents (METs)	12.5±3.1	11.1±2.9	7.4±2.9	0.019	< 0.0001
Systolic BP Rise (mmHg)	46±15	50±18	11±18	0.25	< 0.0001
% Of Predicted Mets (%)	133±38	106±33	82±41	< 0.0001	0.001
Peak Heart Rate (bpm)	153±16	143±21	136±25	0.02	0.14
% Peak Heart Rate (%)	93±13	78±24	84±13	< 0.0001	0.13

LVEDVI: Left Ventricular End-Diastolic Volume Index, LVESVI: Left Ventricular End-Systolic Volume Index, EF: Ejection Fraction, BP, Blood Pressure, NYHA: New York Heart Association

3.4.1 VHD PATIENTS WITH NORMAL EXERCISE ECHOCARDIOGRAMS

Sixty-four VHD patients (56%) had normal stress echocardiograms. Most patients with AR had normal studies. In contrast only 4 patients (15%) with mitral stenosis had a normal stress echocardiogram (Table 3.1). Although patients with VHD and normal exercise echocardiograms were younger than controls (48 ±15 vs. 55±15 years; p=0.02), they had lower exercise capacity (11.1±2.9 vs 12.5±3.1 METS; p=0.02). In addition patients with VHD and normal stress echocardiograms had larger left atria, larger left ventricles at rest and post exercise and higher PAP at rest and post exercise than controls (Table 3.1)

3.4.2 VHD PATIENTS WITH ABNORMAL STRESS ECHOCARDIOGRAMS

Fifty-one patients (44%) with had abnormal stress echocardiograms and were older than those with VHD patients and normal exercise echocardiograms (58±15 vs. 48±15 years; p<0.0001). However these patients were not older than the control group. Patients with abnormal stress echocardiograms had larger left atria, larger ventricles and higher PAP compared to patients with VHD and normal stress echocardiograms.

3.4.3 SYMPTOMATIC STATUS

Eighty-one patients were assessed in NYHA class 1. However despite being asymptomatic they had worse exercise capacity than control subjects (10.3±3.4 vs. 12.5±3.1 METS; p=0.001). Patients with NYHA class 2 symptoms had a lower exercise capacity than those in NYHA class 1 (7.2±2.3 vs. 10.3±3.4, p<0.0001) despite only 2 patients (with equivocal symptoms) having evidence of severe disease

at rest (5% vs. 43%, p <0.0001). Five patients (6%) who were deemed to be asymptomatic at baseline had an exercise capacity of less than 5 METS. Twenty-eight patients (82%) who were deemed to be symptomatic had an exercise capacity greater than 5 METS. However when exercise capacity was stratified according to age, 30 (37%) asymptomatic patients achieved less than 85% of their age-predicted exercise capacity. In contrast 14 (41%) patients who were classed as symptomatic achieved more than 85% of their age predicted METS. Overall the use of objective exercise capacity (workload>85% age-predicted METS) resulted in the re-classification of symptomatic status in 38% of patients. Reclassification of symptomatic status was seen most frequently in patients with AR and MS suggesting that accurate assessment of symptomatic status is most difficult in these groups of patients.

3.4.4 OUTCOME DATA

There were 3 deaths, 4 hospital admissions for heart failure and 24 patients underwent surgery during the 2-year follow up period (Table 3.2). Patients with an abnormal exercise test were more likely to die or be hospitalised with heart failure during follow up (12% vs. 2%, p=0.03). Exercise induced pulmonary hypertension was the only isolated adverse feature on exercise testing that was different in patients who died or those who underwent surgery during follow up (Table 3.2).

Patients who were admitted to hospital had lower exercise capacity, higher pulmonary artery pressure and a lower blood pressure rise with exercise. In contrast poor contractile reserve (a rise in EF of ≤4 %) did not identify patients with adverse

outcome. Exercise capacity was the single best predictor of death or heart failure admission.

Patients with an abnormal stress echocardiogram were more likely to meet the primary endpoint of death or hospitalisation (Figure 3.1) but not the combined end point of death, hospitalisation or need for surgery during follow up (Figure 3. 2).

3.4.5 COMPARISON BETWEEN DIFFERENT VALVE LESIONS.

Patients with an established indication for surgery were excluded from this study. In keeping with the inclusion of some patients with degenerative aortic stenosis, these patients were significantly older than the patients in other valve groups (Table 4). Patients with stenotic valve lesions had a lower rise in systolic blood pressure than those with regurgitant valve lesions (AS 16 ± 23, MS 14 ± 15, AR 59 ± 18, MR 34 ± 19mmHg; $p<0.0001$). Patients with MS were the most likely to have exercise limitation with 88% of patients failing to achieve >85% of their age-predicted exercise capacity. However symptomatic status at rest did not correspond to exercise capacity on exercise stress echocardiography in almost a third of patients regardless of underlying valve lesion (Table 3.4)

Table 3.2. Relative proportions of patients with adverse features on stress echocardiography with adverse outcome

	Death		**Admission**		**Surgery**		**Death/Admission**		**Any Outcome**	
	n (%)	**p**	**n (%)**	**p**	**n (%)**	**p**	**n (%)**	**p**	**n (%)**	**p**
Abnormal BP	2 (5)	0.22	4 (10)	0.005	10 (26)	0.37	6 (15)	0.003	15 (38)	0.02
Normal BP	1 (1)		0 (0)		14 (18)		1 (1)		14 (18)	
METS<5	0 (0)	0.55	3 (25)	<0.0001	1 (8)	0.26	3 (25)	0.004	3 (25)	0.99
METS>5	3 (3)		1 (1)		23 (22)		4 (4)		26 (25)	
PAP>60 mmHg	2 (8)	0.05	2 (8)	0.14	7 (29)	0.27	4 (17)	0.01	10 (42)	0.04
PAP<60 mmHg	1 (1)		2 (2)		17 (19)		3 (3)		19 (21)	
Abnormal ESE*	2 (4)	0.45	4 (8)	0.03	12 (23)	0.59	6 (12)	0.03	17 (33)	0.009
Normal ESE	1 (2)		0 (0)		12 (19)		1 (2)		12 (19)	
EF Increase ≤4%	1 (3)	0.82	1 (3)	0.90	5 (17)	0.57	2 (7)	0.95	5 (17)	0.22
EF Increase >4%	2 (2)		3 (3)		17 (20)		5 (6)		22 (26)	

*Abnormal ESE is at least one of BP rise<20mmHg, Exercise tolerance <5 Mets or PAP post exercise>60mmHg.

BP: Blood Pressure, METs: Metabolic equivalents, PAP: pulmonary artery pressure, ESE: exercise stress echocardiogram, EF: Ejection fraction

Table 3.3 The predictive accuracy of exercise stress echo parameters for clinical outcomes during follow-up.

	Death		Admission		Death/Admission		Operation		Any Event	
	AUC	**p**	**AUC**	**p**	**AUC**	**p**	**AUC**	**p**	**AUC**	**p**
Exercise Capacity (METs)	0.73 (0.57, 0.89)	0.005	0.94 (0.93, 0.96)	<0.0001	0.86 (0.76,0.96)	<0.0001	0.58 (0.46, 0.69)	0.21	0.65 (0.54, 0.76)	0.007
BP Rise (mmHg)	0.52 (0, 1.0)	0.92	0.86 (0.78, 0.93)	<0.0001	0.72 (0.49,0.95)	0.07	0.51 (0.36, 0.66)	0.90	0.58 (0.45, 0.71)	0.22
Post Exercise PAP (mmHg)	0.50 (0, 1.0)	1.0	0.73 (0.58, 0.87)	0.002	0.66 (0.36,0.96)	0.30	0.56 (0.40, 0.72)	0.44	0.58 (0.43, 0.73)	0.30
Change in EF (%)	0.41 (0, 0.83)	0.68	0.31(0, 0.64)	0.25	0.35 (0.10, 0.59)	0.22	0.55 (0.43, 0.67)	0.43	0.46 (0.34, 0.58)	0.48

METs: metabolic equivalents, BP: blood pressure, PAP: pulmonary artery pressure, EF: ejection fraction

Table 3.4 Patient characteristics and exercise data for patients with different valve lesions

	Controls	Aortic Regurgitation	Aortic Stenosis	Mitral Regurgitation	Mitral Stenosis	P value (all valve vs controls)	P value (Comparison between subgroups)
Number of subjects	39	35	28	26	26		
Age (Mean ± SD)	55.4 ± 15.1	43.5 ± 13.5	66.0 ± 9.0	52.7 ± 14.5	50.1 ± 14.8	0.3707	<0.0001
NYHA Class, n (%)	-	3 (9)	11 (39)	10 (38)	10 (38)	0.0001	0.0137
Exercise Capacity	12.5 ± 3.1	11.2 ± 3.5	9.6 ± 3.0	9.8 ± 2.3	6.5 ± 2.8	<0.0001	<0.0001
% peak Heart rate	93 ±13	77 ± 11	84 ± 12	90 ± 10	87 ± 13	<0.0001	0.0002
BP rise	46 ± 15	59 ± 18	16 ± 23	34 ± 19	14 ± 15	0.0002	<0.0001
METS <5, n (%)	0 (0)	1 (3)	0 (0)	0 (0)	12 (46)	0.0395	<0.0001
METS <85% predicted, n (%)	4 (10)	12 (34)	5 (18)	10 (38)	23 (88)	0.0002	<0.0001
Change in NYHA (all), n (%)	-	13 (37)	8 (29)	10 (38)	13 (50)	<0.0001	0.4490
NYHA 1 to 2, n (%)	-	11 (31)	1 (4)	5 (19)	13 (50)	0.0004	0.0010
NYHA 2 to 1, n (%)	-	2 (6)	7 (25)	5 (19)	0 (0)	0.0215	0.0091

Figure 3.1. Kaplan-Meier curves showing event-free survival (death or hospitalisation with heart failure) for patients with a normal stress echocardiogram (blue line) and an abnormal stress echocardiogram (red line) over 2 year follow up (p=0.01)

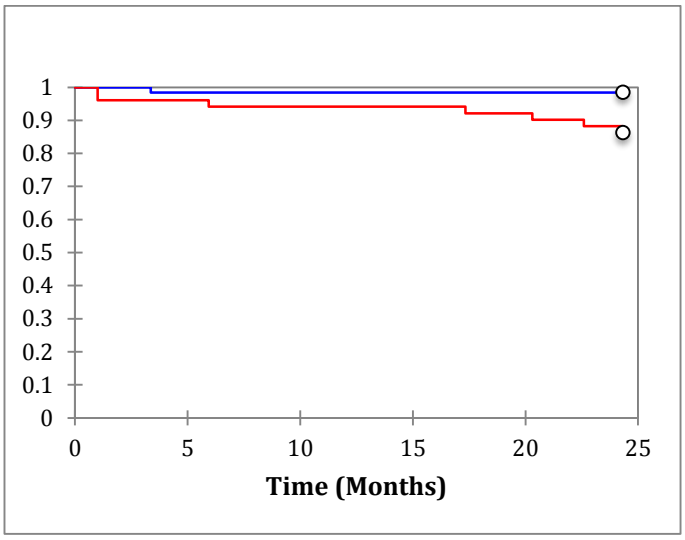
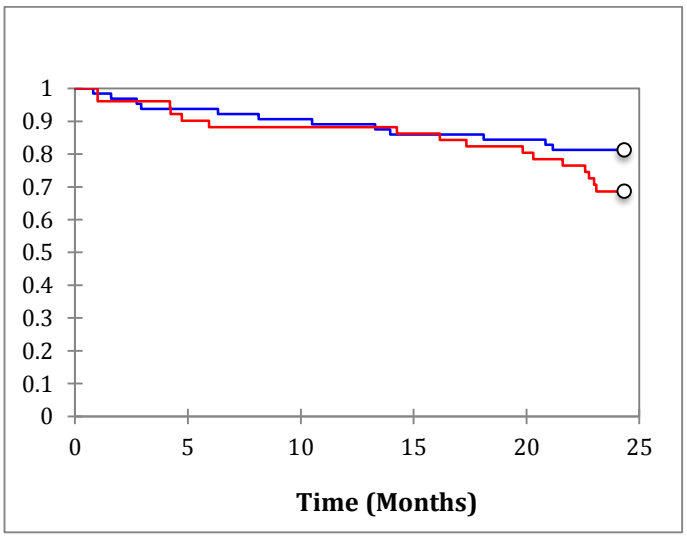


Figure 3.2. Kaplan-Meier curves showing event free survival (death or hospitalisation with heart failure, valve surgery) for patients with a normal stress echocardiogram (blue line) and an abnormal stress echocardiogram (red line) over 2 year follow up (p=0.19)



3.5 DISCUSSSION

This study demonstrates that adverse features found on stress echocardiography in patients with common forms of valvular heart disease are associated with a worse prognosis during a 2-year follow-up period. This is despite these patients not fulfilling any criteria for surgical intervention at the time of enrolment. In particular patients with exercise induced pulmonary hypertension were more likely to die during follow-up. Patients with at least one adverse feature on stress echocardiography were more likely to be hospitalised with heart failure or meet the combined of endpoint of death and heart failure admission.

3.5.1 PREVIOUS STUDIES OF EXERCISE TESTING IN VHD

A number of other studies have assessed the role of exercise testing in valvular heart disease. Most evidence is in asymptomatic patients with severe AS and relates primarily to exercise electrocardiography (ECG). Previous studies have suggested that an abnormal exercise test defined as the development of symptoms, ST depression or a failure to augment blood pressure by >20 mmHg predicted the future onset of symptoms [Alborino *et al* 2002, Amato *et al* 2001] and sudden cardiac death during follow up [Amato *et al* 2001]. More recently a study by Das et al [Das *et al* 2005] confirmed the finding that the development of symptoms with exercise was superior to clinical history and resting echocardiography in predicting future onset of symptoms. However they also found that that the presence of an abnormal BP response to exercise was less helpful. The additional value of exercise stress echocardiography over exercise ECG is less clear. Lancellotti et al and Marechaux et

al found that an exercise induced increase in mean pressure drop across the aortic valve of more than 18 or 20 mmHg respectively was associated with an increased risk of symptom onset or death [Lancellotti *et al* 2005, Marechaux *et al* 2010]. However in patients with reduced LV functional reserve, the ability to generate a significant pressure drop across a stenotic valve may be reduced and this finding should be interpreted with caution. The role of exercise echocardiography in aortic regurgitation is even less clear. A few studies have looked at the presence of exercise induced LV dysfunction in patients with AR. Wahi et al found that a failure to augment LV systolic function at peak exercise was predictive of left ventricular decompensation [Wahi *et al* 2000]. In addition we have previously demonstrated that even in AR patients who have an appropriate increase in EF with exercise, assessment of global longitudinal strain post exercise can detect early LV dysfunction [Gabriel *et al* 2008].

Similarly in MR a number of studies have demonstrated that mitral regurgitation can worsen with exercise and that the absence of contractile reserve is associated with reduced event-free survival and can predict early postoperative LV dysfunction [Magne *et al* 2010, Magne *et al* 2014]. Exercise echocardiography was formally a class 1 recommendation in asymptomatic patients with moderate or severe MS and symptomatic patients with mild MS [Bonow *et al* 2006]. However there are no outcome data to support this and it is a level of evidence C.

3.5.2 CLINICAL ASSESSMENT AND OBJECTIVE EXERCISE CAPACITY

In this study, patients who were deemed to be asymptomatic by clinical assessment alone did indeed have a better objectively measured exercise capacity than those who were symptomatic. The asymptomatic group had a much greater proportion of patients with severe VHD although, in accordance with current guidelines, symptomatic patients with severe valve disease were excluding from undergoing stress echocardiography. It was striking that despite thorough clinical assessment by an experienced cardiologist, a significant number of apparently asymptomatic patients had extremely poor exercise capacity when subjected to exercise stress echocardiography and that reclassification of symptomatic status occurred in a third of patients across all valve groups. This is in keeping with the findings of other studies, which have highlighted the difficulty in the accurate assessment of symptomatic status in patients with valve disease.

Previous guidelines [Bonow *et al* 2006] recommended exercise stress echocardiography for asymptomatic patients with severe AS (peak velocity >4 m/s or mean gradient >40 mmHg), in asymptomatic moderate or severe MS (MVA <1.5 cm^2) and symptomatic patients with mild MS. For patients with MS, a rise in PAP of >60 mmHg or a pulmonary capillary wedge pressure (PCWP) of >25 mmHg was considered an indication for intervention. However the most recent ACC/AHA [Nishimura *et al* 2014] guidelines no longer specifically consider exercise induced pulmonary hypertension as a criteria to intervene but instead prompt the clinician to reassess the patient's symptomatic status. Stress echocardiography is now only considered a class 1 indication in patients in whom there is a discrepancy between

symptom status and clinical assessment and Doppler echocardiographic markers of severity at rest [Nishimura *et al* 2014]. Exercise stress echocardiography is recommended in patients with chronic MR where there is a discrepancy between symptoms and severity at rest. In addition they suggest that exercise treadmill testing can be useful to establish symptoms status and exercise tolerance. No specific recommendations are made for stress echocardiography in AR other than it may be helpful to define symptom status.

3.5.3 ABNORMAL STRESS ECHOCARDIOGRAMS AND ADVERSE OUTCOME

Patients with an established indication for surgery were excluded from this study in keeping with current guidelines. Consequently given that in some cases intervention is now considered at an earlier stage for patients with valve disease, the patients in this study consist of a lower risk cohort than in previously published studies. This may be reflected in the lower than expected event rate during follow up. However despite this we found a significantly poorer outcome across a range of different valvular heart lesions for patients with an abnormal exercise stress echocardiogram. Although the best single predictor was an exercise capacity of <5 METS, the addition of a poor BP response to exercise and exercise induced pulmonary hypertension (PAP >60 mmHg) offered incremental prognostic information and was clearly associated with an increased rate of death or admission with heart failure over the 2-year follow up period. Conversely the measurement of contractile reserve (CR) as assessed by change in EF is probably not helpful and should not be considered routinely.

These findings suggest that stress echocardiography, with the measurement of pulmonary pressure post exercise should be considered more frequently in the assessment of asymptomatic patients with VHD. It remains unclear whether earlier intervention following a positive exercise stress echocardiogram can improve the long-term outcome of these patients. Although this needs to be the subject of future research, it remains difficult to investigate this as in clinical practice, patients with adverse features on exercise stress echocardiography, particularly those with poor exercise capacity will have their symptomatic status re-classified and may require referral for valve surgery.

3.5.4 CHOICE OF EXERCISE PROTOCOL

We performed exercise stress echocardiography using a treadmill rather than a semi-supine ergometer. The cycle ergometer has a number of advantages in the assessment of VHD. In particular it allows images to be obtained during exercise, thereby allowing additional measurements such as changes in valve gradients or quantitative assessment of MR severity during exercise to be obtained. However cycle ergometers are not widely available outside mainland Europe. In addition to their widespread availability, treadmill exercise has a number of other advantages. Firstly it is more physiological and patients are more readily able to equate performance on a treadmill to their exercise capacity in day-to day activities. Secondly, patients are often able to achieve higher workloads and higher heart rates with treadmill exercise. This was demonstrated by the fact that most patients achieved >85% of their maximum heart rate during this study. However when using treadmill exercise with a standard Bruce protocol for the MR cohort, we found

significant clustering of patients' exercise times that coincided with the end of each 3-min stage of the standard Bruce protocol. This probably represents a goal-orientated approach to exercise and perhaps affects the true objective determination of exercise capacity. Consequently for other valve groups we adapted the Bruce protocol such that the speed and/or incline increased at 1-min intervals. The protocol was adapted to ensure that the exercise capacity in METs at the end of each 3-min interval remain unchanged when compared to the standard Bruce protocol (Appendix 1). This resulted in a more even spread of exercise times across VHD patients. This suggests that when using treadmill exercise in order to objectively assess exercise capacity, the use of a more graduated protocol such as the one used in this study should be considered.

3.5.5 STUDY LIMITATIONS

This study did not specifically assess the role of more detailed PISA based markers of severity during exercise in MR or increased valve gradients with exercise in AS which have previously been shown to predict outcome [Magne *et al* 2010, Marechaux *et al* 2010]. In addition we did not assess the role of global longitudinal strain post exercise which may identify a higher risk cohort of patients with VHD [Magne *et al* 2014]. Although feasible, these markers are much more difficult to assess particularly during exercise and as above requires the use of a semi-supine tilting ergonometer to perform reliably. Furthermore it is difficult to compare these variables across different types of valve lesions. Instead we chose to focus on easily measurable and directly comparable variables such as exercise capacity, BP rise with exercise, and PAP. Although we also assessed the presence of CR, defined by a

change in EF post exercise, this was not predictive of adverse outcome. Measurement of exercise capacity, BP response to exercise and PAP is straightforward and hence more readily incorporated into clinical practice. A further limitation is that although the total number of patients within the study is reasonable, the number of adverse events during follow up was lower than expected. This may reflect the overall low-risk cohort of patients recruited within the study. Given the low rate of adverse events it was not possible to perform regression analysis to determine the effect of other predictors such as age and sex on adverse outcome. Although patients with an abnormal stress echocardiogram were older than those with a normal stress echocardiogram, the patients within this cohort, most of whom had severe VHD, were typically younger than seen in many valve clinics due to the high prevalence of rheumatic fever. In addition the number of patients within each valve group is relatively small and hence detailed comparison between valve lesions is not possible.

3.6 CONCLUSION

The clinical assessment of symptomatic status is unreliable and a significant number of patients with VHD who do not meet the criteria for surgery based on clinical assessment and resting echocardiography perform badly during exercise stress echocardiography. The finding of an abnormal exercise echo is predictive of an increased risk of death or hospitalisation with heart failure the next 2 years. Exercise stress echocardiography or if not available exercise ECG should be considered as part of the routine follow up of asymptomatic patients with VHD.

3.7 ACKNOWLEDGEMENTS

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CHAPTER FOUR

NATRIURETIC PEPTIDES IN MITRAL STENOSIS

Sharma V, Stewart RA, Zeng I *et al.*
Comparison of atrial and brain natriuretic peptide for
the assessment of mitral stenosis.
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4.1 SUMMARY

Accurate evaluation of the functional consequences of mitral stenosis (MS) can be difficult. The aim of this study was to evaluate the relationship between both atrial (ANP) and brain natriuretic peptides (BNP) and symptoms, exercise capacity and echocardiographic measures of MS severity. Thirty patients with moderate to severe MS and 14 normal controls underwent clinical assessment, exercise stress echocardiography, measurement of ANP and BNP and 2 years follow up for clinical events. BNP was higher in MS patients than controls (BNP 58 [IQR 34,93] vs. 16 [14,25], $p<0.0001$). There was considerable overlap in exercise capacity and echocardiographic severity between asymptomatic and symptomatic patients. An increase in BNP was associated with a larger left atrial area index ($r=0.67, p<0.0001$), reduced mitral valve area ($r = -0.38$, $p=0.05$) and higher resting pulmonary artery pressure ($r=0.47$, $p=0.008$). Increased BNP predicted lower treadmill exercise capacity (AUC =0.82 [95% confidence interval 0.67,0.97], $p=0.004$), guideline criteria for intervention (AUC=0.87 [0.74,0.99], $p=0.006$) and adverse events during follow up (AUC=0.81 [0.64,0.99], $p=0.03$). Associations for ANP in general were similar but slightly weaker, and ANP did not provide additional predictive information to BNP. BNP may improve risk stratification of patients with MS, particularly when symptoms are equivocal.

4.2 INTRODUCTION

The commonest cause of mitral stenosis (MS) worldwide is rheumatic fever. Typically there is an extremely long latent period during which the disease progresses slowly. Consequently defining the onset of symptoms can be extremely difficult. However patients who are asymptomatic or mildly symptomatic may be at risk of adverse haemodynamic consequences including pulmonary hypertension and atrial arrhythmias [Olesen 1962, Wood 1954]. The early identification of such patients may decrease the risk of stroke, acute decompensation, right ventricular failure and identify the need for surgery or percutaneous intervention.

4.2.1 MANAGEMENT OF PATIENTS WITH MS

Current ACC/AHA guidelines [Bonow *et al* 2006] recommend percutaneous mitral balloon valvotomy (PMBV) in symptomatic patients with moderate or severe MS and or asymptomatic patients when pulmonary artery pressure is >50 mmHg at rest or >60 mmHg post exercise if the mitral valve morphology is suitable. Application of these guidelines requires regular specialist review with echocardiography during follow-up, often for many years. However rheumatic heart disease is most prevalent in poor and geographically remote communities that may have limited access to regular specialist medical care. Consequently a simple low cost method for monitoring patients with known MS in the community, which could identify patients at greater risk of adverse events, would be extremely valuable.

4.2.2 NATRIURETIC PEPTIDES IN MS

It is known that plasma BNP concentrations are elevated in conditions that result in increased left ventricular wall stress and it use has been proposed as a test of exclusion for left ventricular dysfunction [Levin *et al* 1998, Richards *et al* 1998]. However in MS the left ventricle is protected from increased left ventricular wall stress by the stenotic mitral valve. Consequently the haemodynamic situation in patients with significant MS differs to that found in other valve lesions which usually result in increased left ventricular wall stress and/or pressure. Despite this however a few studies have reported an association between BNP and resting echocardiographic measures of severity [Arat-Ozkan *et al* 2005, Eryol *et al* 2007, Iltumur *et al* 2005, Selcuk *et al* 2007]. Atrial natriuretic peptide (ANP) however is released predominantly in response to increased atrial wall stress, and might therefore be more useful in the monitoring of patients with MS [Ferrari and Agnoletti 1989]. Several very small studies have reported associations between ANP and left atrial pressure, mitral valve gradient and pulmonary artery pressure in mitral stenosis [Ishikura *et al* 1991, Nishikimi *et al* 1986, Tsai *et al* 1990], and one reported that ANP but not BNP predicted left atrial pressure in MS [Nakamura *et al* 1992].

4.2.3 STUDY AIMS

This aim of this study is to determine whether the measurement of ANP or BNP provides additional information compared to standard assessment of symptomatic status and echocardiographic severity in mitral stenosis. In addition we evaluated the ability of natriuretic peptides to identify patients with ACC/AHA guideline criteria

for balloon mitral valvotomy and to predict adverse clinical outcomes during 2 years of follow-up.

4.3 METHODS

4.3.1 STUDY POPULATION

Patients with mitral stenosis were initially identified from echocardiogram reports and outpatient clinics in the Auckland region as described in section 2. Exclusion criteria included greater than mild concomitant valvular lesions, previous valve replacement surgery, previous myocardial infarction, poor echocardiographic images, regional wall motion abnormalities on echocardiography, left ventricular impairment (LV ejection fraction<50%), significant renal impairment (creatinine >0.16mmol/L), respiratory disease or an inability to walk on a treadmill. Control subjects were volunteers from the local community who had no history of cardiac or respiratory disease and were age and sex matched.

4.3.2 ECHOCARDIOGRAPHY

All patients underwent comprehensive echocardiography as outlined in Section 2. The mitral valve area (MVA) was obtained using direct planimetry, pressure half time, proximal isovelocity area and continuity methods [Hatle *et al* 1978, Martin *et al* 1979, Nakatani *et al* 1988]. The median MVA from these four methods was used for analysis. Mean trans-mitral pressure gradients were obtained by tracing the continuous wave Doppler signal across the mitral valve [Quinones *et al* 2002]. The

left atrial area was measured in the apical four-chamber view [Lester *et al* 1999]. The left ventricular end-diastolic and end-systolic volumes and ejection fraction were measured from the apical four-chamber view using the modified Simpson's single plane method. This method was chosen to allow comparison with the post exercise volumes. RV area was obtained by measuring the RV end diastolic area in the apical four-chamber view. Resting and exercise right ventricular function was assessed from the peak systolic tricuspid annular velocity (RV S') [Lang *et al* 2005]. Left atrial area, left ventricular volumes, and right end diastolic area were indexed to body surface area [DuBois and DuBois 1916]. All echocardiographic analysis was completed prior to analysis of the blood samples and blind to clinical and outcome data.

4.3.3 ESTIMATION OF PULMONARY ARTERY PRESSURE

To facilitate estimation of RV systolic pressure, agitated saline was injected to enhance the tricuspid regurgitation profile as described in section 2 [Himelman *et al* 1990]. The peak PAP was derived using the simplified Bernoulli equation from the peak tricuspid regurgitant jet and added to an estimate of right atrial pressure obtained from imaging of the inferior vena cava [Otto 2000].

4.3.4 TREADMILL EXERCISE AND POST-EXERCISE ECHOCARDIOGRAPHY

Exercise tests were performed using a modified ramped exercise protocol in which the speed and gradient of the treadmill increased at one minute intervals [Van Pelt *et al* 2007]. The workload at the end of each 3-min interval was equivalent to the

standard Bruce protocol. Continuous 12-lead ECG monitoring was performed with blood pressure recordings taken at 2 min and then every 3 min. Exercise was stopped for significant dyspnoea, chest discomfort, pre-syncope and fatigue, or at patient request.

Immediately after exercise, echocardiographic images were obtained in the apical four-chamber view, first for LV volumes, then continuous wave Doppler across the mitral valve to obtain mean mitral valve gradient and finally for tricuspid jet velocity with agitated saline enhancement. All data was obtained within one minute of peak exercise.

4.3.5 MEASUREMENT OF NATRIURETIC PEPTIDES

Fasting blood samples were obtained from an indwelling intravenous catheter after 15 min lying supine, immediately prior to the baseline echocardiogram. Blood samples were collected in EDTA tubes, centrifuged and plasma stored at –80 ºC. BNP and ANP concentrations were measured at study end using established radioimmunoassays [Yandle *et al* 1993]. The upper limit of the normal laboratory reference range for BNP is 42 pg/mL and for ANP 83 pg/mL [Yandle *et al* 1993]. To convert natriuretic peptide levels expressed in pg/mL to pmol/L, divide by 3.47 for BNP and 3.08 for ANP. All clinical, echocardiographic, exercise and outcome assessments were performed blind to natriuretic peptide data.

4.3.6 ASSESSMENT OF STUDY OUTCOMES

Patients underwent regular clinical follow up by their usual cardiologist who also decided the requirement for, and timing of mitral valvotomy or valve replacement, blinded to peptide levels and exercise echo data. Follow up data was collected for 2 years from the date of enrolment, except for one patient who moved overseas and was lost to follow-up. Outcomes obtained were death, referral for valve intervention and heart failure requiring hospitalisation. The primary clinical outcome was a composite of these events.

Low exercise capacity was defined as <5 metabolic equivalents (METS) on treadmill exercise [Fletcher *et al* 1995, McCully *et al* 2002]. This also represented approximately 2 standard deviations below the mean for the age and sex matched normal controls.

Consideration of percutaneous mitral balloon valvotomy (PMBV) in patients with moderate to severe MS (MVA<1.5 cm^2) who are either symptomatic, have low exercise capacity, pulmonary hypertension (PAP >50mmHg at rest or >60 mmHg after exercise) or raised PCWP (>25 mmHg) is a Class 1 recommendation in the current ACC/AHA guidelines [Bonow *et al* 2006]. With the exception of PCWP (which was not measured), peptide levels were assessed against each component of the guideline separately and also the combined guideline. The suitability of the mitral valve for valvotomy was not considered in the analysis.

4.3.7 STATISTICAL ANALYSIS

Two sample student t-tests or Mann Whitney U test were used for comparing continuous variables between patients and controls. Chi square tests or Fisher exact tests were used to assess the associations between categorical variables. Pearson or Spearman correlation coefficients were used to assess associations between continuous variables. Analysis of Variance (ANOVA) was performed to assess the differences in the mean echocardiographic and exercise parameters across different BNP/ANP range groups. Post hoc Tukey Honest Significant Difference (HSD) tests were applied for checking multiple comparisons across groups but did not correct for variables-wise multiple testing. Levene's Tests were used to examine group homogeneity. Kruskal-Wallis test was used where the homogeneity assumption did not hold. BNP and ANP underwent natural log transformations and non-transformed data are reported as median and inter-quartile range.

For descriptive analyses MS patients were divided into three groups according to whether BNP was within the normal reference range (<42 pg/mL), above the normal range (42 to 84 pg/mL) or more than twice the upper limit of normal (≥84 pg/mL). Equivalent cut levels for ANP were 83 and 166 pg/mL.

Logistic regressions were undertaken for natriuretic peptide levels to predict different binary endpoints. Prediction accuracies were reported by area under the receiver operating characteristic curve (AUC) and its 95% confidence interval. To assess the predictive value of the combination of ANP and BNP, the peptide levels were first adjusted to provide equal weighting (using results from normal controls) and then

summed. Kaplan Meier curves were used to visualize the time to first clinical event across different natriuretic peptide range groups. SAS released 8.0 software (SAS Institute Inc., Cary, NL, USA) was used for analysis. All tests were two tailed and a p-value of 0.05 was considered statistically significant.

4.4 RESULTS

In order to determine whether plasma BNP could identify patients with haemodynamically significant MS, MS patients were stratified according to whether their BNP concentration was within the normal range (42 pg/mL), the intermediate range (42–84 pg/mL) or high range (>84 pg/mL). High BNP was defined as >2 times the upper limit of normal. The clinical, echocardiographic and treadmill data for normal controls and for patients with MS stratified by plasma BNP are presented in Table 4.1.

4.4.1 COMPARISON OF PATIENTS VERSUS CONTROLS

Plasma BNP concentrations were significantly higher in patients with MS compared to controls (BNP 58 [34, 93] vs. 16 [14, 25] pg/mL, $p < 0.0001$). Similarly plasma ANP concentrations were also higher in MS patients compared to controls (ANP 111 [82, 188] vs. 43 [32, 50] pg/mL, $p < 0.0001$).

Compared to controls, MS patients with BNP concentrations within the normal range had a larger left atrial area (11±2 vs. 15±2 cm^2/m^2, $p<0.001$), higher PAP at rest (23±4 vs. 34±16 mmHg, $p = 0.004$) and higher PAP post-exercise (40±8 vs. 55±24 mmHg, $p = 0.04$). In addition patients with MS in whom plasma BNP remained within the normal ranges had a reduction in exercise capacity compared to controls (11±3 vs. 8±3 METS, $p = 0.006$). These observations imply that cardiac remodeling and early dysfunction can occur in MS without a significant increase in BNP.

Table 4.1. Baseline characteristics and resting echocardiographic measurements in normal controls and mitral stenosis patients with BNP concentrations within, above and more than twice the laboratory upper limit of the normal reference range (mean, standard deviation or n, %)

	Controls	**MS and Normal BNP (<42 pg/mL)**	**MS and High BNP (42–84 pg/mL)**	**MS and High BNP (≥ 84 pg/mL)**	**p value**
Number Of Subjects	14	10	11	**9**	**-**
Age (years)	51 (14)	50 (14)	47 (14)	50 (16)	0.90
Patient Characteristics					
Female n (%)	10 (71%)	10 (100%)	9 (82%)	9 (100%)	0.31
Body Mass Index (kg/m^2)	26.8 (3.9)	27.4 (5.4)	29.7 (5.7)	28.5 (6.7)	0.67
Atrial Fibrillation	0	1 (10%)	1 (9%)	6 (67%)	0.006
NYHA Class >1	0	3 (30%)	4 (36%)	7 (78%)	0.09
Medication					
Loop Diuretic	0	3(30%)	4(36%)	4(50%)	0.80
ACE Inhibitor	0	1 (10%)	2 (18%)	1 (11%)	>0.90
Beta Blocker	0	1 (10%)	2 (18%)	1 (11%)	>0.90
Echocardiography at rest					
LA Area Index (cm^2/m^2)	10.7 (1.9)	15.2 (1.7)	18.7 (3.2)	24.5 (7.8)	0.0009
MV Area (cm^2)	-	1.4 (0.2)	1.2 (0.3)	1.1 (0.1)	0.02
MV Area Index (cm^2/m^2)	-	0.8 (0.2)	0.6 (0.1)	0.6 (0.1)	0.05
Mean MV Gradient (mmHg)	-	6 (5)	8 (4)	10 (4)	0.18
PAP (mmHg)	23 (4)	34 (16)	32 (9)	42 (7)	0.18
LVEDVI (mL/m^2)	45 (8)	45 (7)	49 (9)	34 (12)	0.004
LVESVI (mL/m^2)	15 (6)	17 (5)	19 (6)	13 (5)	0.09
LVEF (%)	67 (7)	64 (8)	62 (8)	62 (6)	0.85
RA Area Index (cm^2/m^2)	9.2 (1.6)	10.5 (1.7)	9.8 (1.9)	14.6 (2.7)	<0.0001
S' Tricuspid Annulus (cm/s)	12 (2)	11 (2)	11 (2)	11 (2)	0.88
RVd Area Index (cm^2/m^2)	11.1 (2.0)	10.6 (1.7)	11.2 (2.0)	10.7 (1.6)	0.69

MS: mitral stenosis, BNP: brain type natriuretic peptide, NYHA New York Heart Association; ACE: angiotensin converting enzyme; LA: left atrial, MV: mitral valve, PAP: pulmonary artery pressure; LVEDVI left ventricular end diastolic volume index, LVESVI: left ventricular end systolic volume index, LVEF: left ventricular ejection fraction, RA: right atrial, RVd right ventricular diastolic

4.4.2 ASSOCIATION OF PLASMA NATRIURETIC PEPTIDE CONCENTRATIONS WITH ECHOCARDIOGRAPHIC AND EXERCISE MARKERS OF SEVERITY IN MS PATIENTS

In MS patients, an increase in BNP was associated with a larger left atrial area index (r= 0.67, p<0.0001), lower exercise capacity (r= −0.56, p=0.001) and higher resting pulmonary artery pressure (r= 0.47, p=0.008). Associations between BNP and mitral valve area (r= −0.38, p=0.05) and systolic blood pressure rise post exercise (r= −0.46, p=0.01) were weaker. There was no association between BNP and right ventricular size or peak tricuspid systolic annular velocity (S') at rest or after exercise. Associations between BNP and different echocardiographic and exercise measurements appeared to be similar for MS patients in sinus rhythm and atrial fibrillation (Figure 4.1).

Plasma concentrations of ANP and BNP were strongly correlated (r= 0.76, p < 0.0001), as illustrated in Figure 4.1. In general associations between ANP and echocardiographic measures of disease severity were similar to those observed for BNP. However ANP was not clearly associated with exercise capacity (r= −0.19, p=0.3) or systolic blood pressure rise during exercise (r= −0.27, p=0.15).

Figure 4.1. Association between the natural log of BNP (lnBNP) and left atrial area index (mL/m^2), exercise capacity (in metabolic equivalents), mitral valve area index (cm^2/m^2), pulmonary artery pressure (mmHg), systolic blood pressure response to exercise (mmHg) and the natural log of atrial natriuretic peptide (lnANP). Normal controls (solid circles), MS patients in sinus rhythm (open circles), MS patients in AF (crosses). Numbers in brackets are BNP level in pg/mL

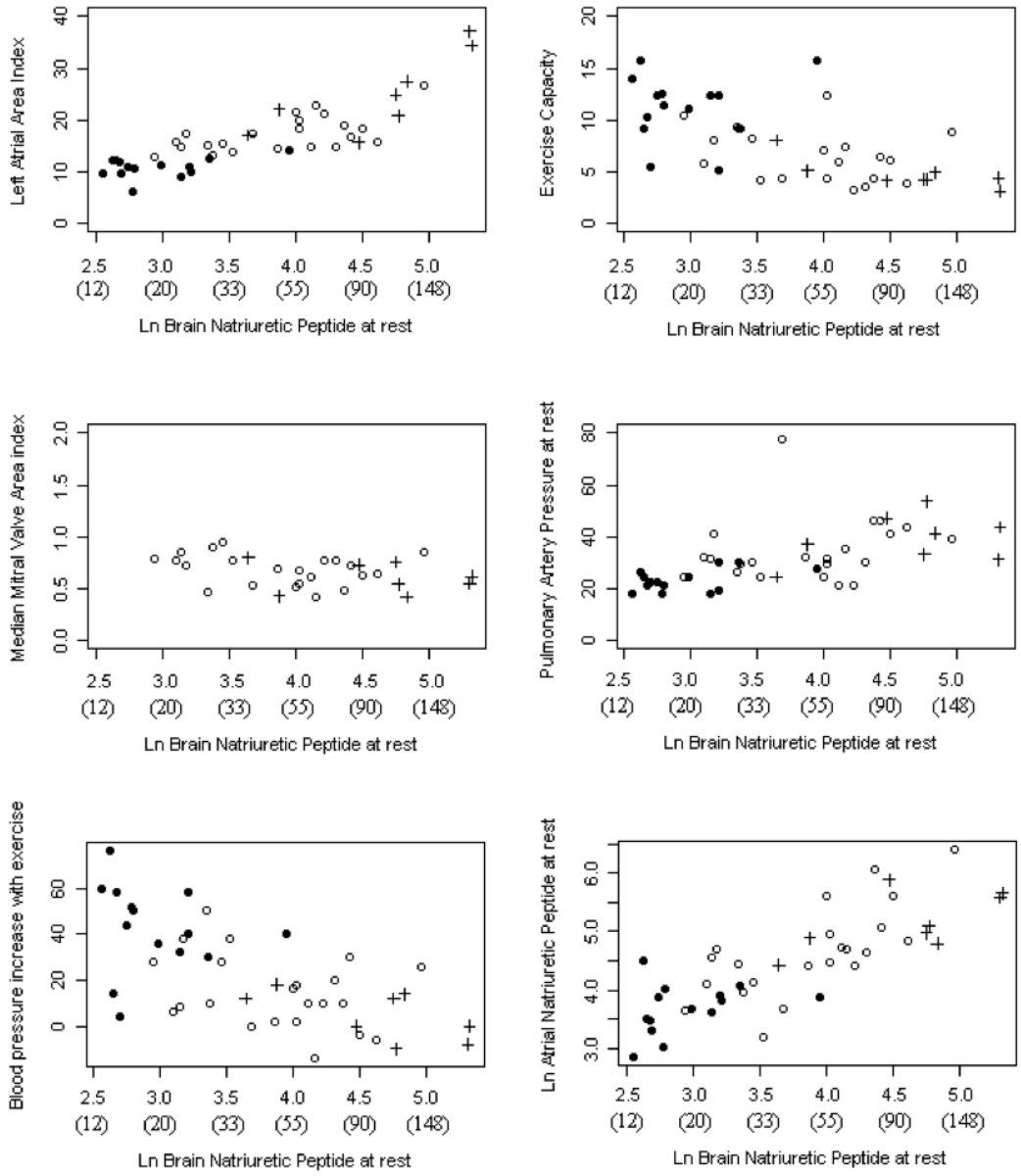


Table 4.2. Exercise stress echocardiography data in normal controls and mitral stenosis patients with BNP levels within, above and more than twice the laboratory upper limit of the normal reference range

Results are mean (standard deviation) or number (%).

BNP: Brain type natriuretic peptide; MV: mitral valve, PAP: pulmonary artery pressure; LVEDVI left ventricular end diastolic volume index, LVESVI: left ventricular end systolic volume index, LVEF: left ventricular ejection fraction, BP: blood pressure

	Controls	**MS and Normal BNP (≤42 pg/mL)**	**MS and High BNP (42–84 pg/mL)**	**MS and High BNP (≥ 84 pg/mL)**	**P value**
Treadmill Exercise					
Peak Heart Rate (bpm)	161 (11)	151 (27)	137 (19)	161 (20)	0.07
Exercise Capacity (METs)	11.2 (3.2)	8.0 (2.6)	6.0 (2.7)	4.9 (1.7)	0.03
Peak Systolic BP (mmHg)	158 (25)	136 (25)	130 (26)	132 (20)	0.84
BP Increase (mmHg)	42 (19)	22 (17)	11 (12)	3 (12)	0.02
Post exercise Echocardiography					
Mean MV Gradient (mmHg)	-	19 (8)	20 (9)	22 (9)	0.84
PAP (mmHg)	40 (8)	55 (24)	52 (12)	67 (14)	0.17
LVEDVI (mL/m^2)	37 (12)	30 (9)	35 (9)	21 (3)	0.002
LVESVI (mL/m^2)	8 (4)	7 (3)	10 (5)	7 (2)	0.27
LVEF (%)	79 (8)	76 (6)	72 (11)	69 (12)	0.27
S' Tricuspid Annulus (cm/s)	21 (4)	19 (6)	16 (3)	16 (5)	0.23

4.4.3 COMPARISON BETWEEN ASYMPTOMATIC AND SYMPTOMATIC MS PATIENTS

The comparison of natriuretic peptide levels, echocardiographic and treadmill data between asymptomatic and symptomatic patients is shown in Table 4.2. Treadmill exercise capacity was similar between symptomatic patients and asymptomatic patients (6±2 vs. 7±3 metabolic equivalents, (METS); p=0.19). Echocardiographic measures of disease severity did not significantly differ between symptomatic and asymptomatic patients, with the exception of resting PAP, which was slightly higher in symptomatic patients. BNP was a stronger predictor of decreased exercise capacity (AUC=0.82 [95% confidence interval 0.67, 0.97], p=0.004) than mitral valve area (AUC=0.62 [0.40, 0.83], p=0.29), resting pulmonary artery pressure (AUC=0.70 [0.50, 0.90], p=0.07) and left atrial area (AUC=0.70 [0.49, 0.89], p=0.08)].

Table 4.3. Comparison of treadmill exercise outcomes, exercise echocardiography and natriuretic peptide levels for asymptomatic and symptomatic patients with mitral stenosis

	Asymptomatic	**Symptomatic**	**p value***
Number Of Subjects	16	14	-
Natriuretic Peptides			
BNP (pg/mL)	52 (31, 73)	82 (49, 118)	0.08
ANP (pg/mL)	89 (71, 142)	129 (108, 286)	0.08
Rest Echocardiography			
LA Area Index (mL/m^2)	18.2 ± 6.	20.5 ± 5.9	0.16
MV Area (cm^2)	1.3 ± 0.2	1.1 ± 0.2	0.21
PAP (mmHg)	32.1 ± 13.6	39.6 ± 7.7	0.01
Exercise Echocardiography			
Exercise Capacity (METs)	7.0 ± 3.0	5.5 ± 2.0	0.19
Mean MV Gradient (mmHg)	18.8 ± 8.0	21.7 ± 8.8	0.36
PAP (mmHg)	51.5 ± 18.0	64.2 ± 14.8	0.02

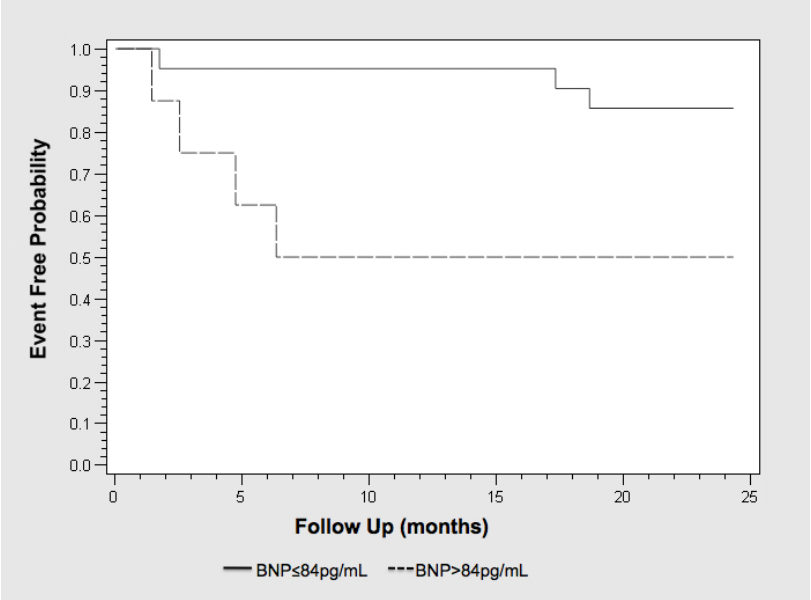
*****Mann Whitney U test. Results are mean ± standard deviation or median (inter-quartile range) BNP: Brain type natriuretic peptide; ANP: atrial natriuretic peptide; LA: left atrial, MV: mitral valve, PAP: pulmonary artery pressure;

4.4.4 PLASMA CONCENTRATIONS OF NATRIURETIC PEPTIDES AS A MARKER OF ADVERSE PROGNOSIS

Seven patients were either referred for valve intervention (*n*=5) and/or had a hospital admission for heart failure (*n*=4) during follow-up. There were no deaths during follow up. Kaplan–Meier curves for the composite of these outcomes according to BNP and ANP concentrations are shown in Figure 4.2. Lower concentrations of BNP and ANP were associated with a reduced rate of valve intervention and heart failure admission during follow- up (*p*=0.02 and 0.002 respectively). One patient with a BNP and ANP within the normal range met the primary endpoint at 17 months.

The predictive values of both BNP and ANP for ACC/AHA criteria for mitral valvotomy and for clinical events during follow-up are presented in Table 4.3. The AUCs for ANP and BNP for adverse events during follow-up were similar. However BNP was more predictive than ANP for an exercise capacity <5 metabolic equivalents, pulmonary hypertension and for guideline criteria for intervention. BNP was able to predict any ACC/AHA criteria for intervention with a reasonably high sensitivity and specificity (AUC=0.87 (0.74, 0.99), *p*=0.006). Combining BNP and ANP levels did not improve the predictive value over BNP alone for any criteria (Table 4.4).

Figure 4.2. Kaplan–Meier plots of time to first clinical event (death, referral for valve intervention or hospital admission with heart failure) for patients with and without a plasma BNP >84 or ≤84 pg/mL and ANP >166 and ≤166 pg/mL. The cut levels are at twice the upper limit of the normal reference range for the laboratory [24]. One patient with an adverse event had a BNP at the upper level of normal (40 pg/mL) and an ANP within the normal range. By log rank test, p=0.02 for BNP, p=0.002 for ANP.



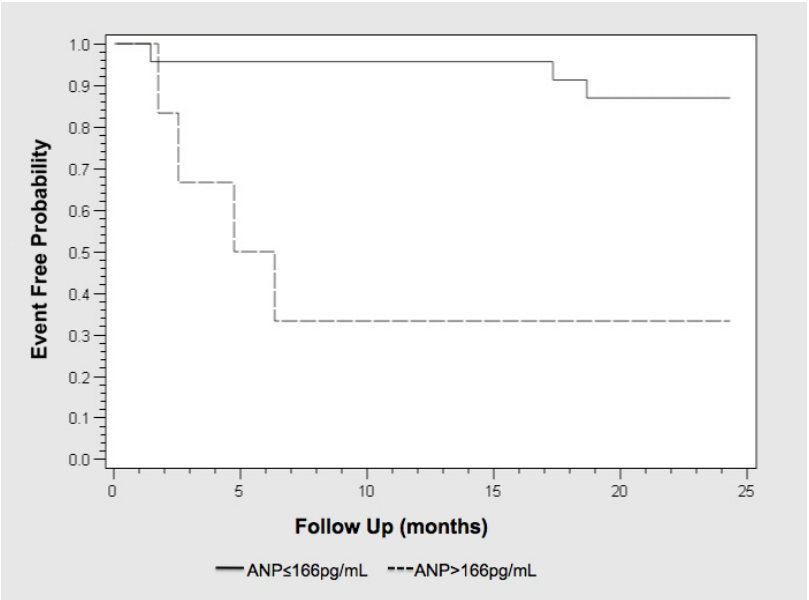


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Table 4.4 The Predictive Accuracy Of BNP And ANP For Different ACC/AHA Guideline Criteria For Balloon Mitral Valvotomy And For Clinical Outcomes During Follow-Up

		BNP*		**ANP***		**ANP and BNP****	
	n	AUC	p	AUC	p	AUC	p
Symptoms	14	0.70 (0.51,0.89)	0.11	0.70 (0.50,0.89)	0.12	0.69 (0.49,0.89)	0.09
Low Exercise Capacity (<5 METS)	13	0.82 (0.67,0.97)	0.01	0.58 (0.37,0.80)	0.65	0.69 (0.50,0.90)	0.14
Pulmonary Hypertension*	10	0.76 (0.56,0.96)	0.05	0.76 (0.56,0.95)	0.07	0.76 (0.56, 0.95)	0.05
Any ACC/AHA Criteria	18	0.87 (0.74,0.99)	0.006	0.76 (0.57,0.94)	0.07	0.80 (0.64,0.96)	0.01
Clinical Outcome	7	0.81 (0.64,0.99)	0.03	0.78 (0.54,1.0)	0.04	0.81 (0.59,0.99)	0.03

AUC: Area Under Receiver Operator Curve Characteristics, ACC/AHA: American College of Cardiology/American Heart Association

4.5 DISCUSSION

In this study, patients with MS and a plasma BNP concentration >84 pg/mL (twice the upper limit of the normal reference range) were more likely to have a low exercise capacity on treadmill exercise and a higher risk of clinical events during follow-up. These patients were also more likely to have a Class I indication for mitral balloon valvuloplasty [Bonow *et al* 2006]. Conversely, although values were higher than controls, patients with a BNP concentration within the normal range (<42 pg/mL) were unlikely to have significant pulmonary hypertension or marked left atrial enlargement. In addition these patients had a low rate of valve intervention or hospitalisation for heart failure during the next two years. These findings suggest that measurement of BNP may assist management decisions for some patients with MS.

In clinical practice symptoms can be difficult to assess because patients gradually adapt over time. Our observation that NYHA status was a poor predictor of exercise capacity or MS severity highlights this important problem. Incorrectly classifying a patient as symptomatic may result in an inappropriate referral for valve intervention, which is associated with significant morbidity and mortality in ~10% of patients [Vahanian *et al* 2007]. An elevated BNP in an apparently asymptomatic patient with mitral stenosis may alert the clinician to haemodynamically significant MS, while a low BNP is more reassuring.

In the current study, most patients with MS had BNP levels below 100 pg/mL: a threshold recommended in the European Society of Cardiology Heart Failure

guidelines to exclude cardiac failure as a cause of dyspnoea [Dickstein *et al* 2008]. This implies that clinically relevant thresholds for BNP are lower in MS than in patients with LV systolic dysfunction.

4.5.1 BNP AND MARKERS OF LA STRETCH

The strong correlation between plasma BNP and left atrial area suggests atrial secretion of BNP in MS. This hypothesis is supported by evidence for synthesis of BNP by atrial myocytes in response to chronic increases in wall stress [Langenickel *et al* 2000] and co-storage of BNP with ANP in atrial granules [Goetze *et al* 2006]. Plasma concentrations of BNP have also been reported to increase with left atrial size in patients with moderate or severe mitral regurgitation and normal LV function [Kerr *et al* 2008]. While increased BNP secretion from the right ventricle is also possible, there was no association between plasma BNP concentration and right ventricular size or systolic function either at rest or post exercise.

4.5.2 COMPARISON OF ANP AND BNP IN MS

Several previous studies have reported similar associations between plasma ANP, BNP and N-terminal pro-BNP and echocardiographic measures of MS severity [Arat-Ozkan *et al* 2005, Eryol *et al* 2007, Iltumur *et al* 2005, Selcuk *et al* 2007]. However, these studies did not include stress echocardiography, an objective assessment of exercise capacity, or evaluation of outcomes during follow-up. They were therefore unable to compare the predictive value of ANP and BNP for several clinically relevant markers of disease severity and prognosis. In the current study BNP and ANP were closely correlated and had similar associations with

echocardiographic measures of severity of MS. However ANP was a poorer predictor of low exercise capacity and did not provide additional predictive information when BNP was known.

4.6 STUDY LIMITATIONS

Study limitations include the relatively small number of patients evaluated and the low number of adverse events during follow-up. Previous studies were also small [Arat-Ozkan *et al* 2005, Eryol *et al* 2007, Iltumur *et al* 2005, Ishikura *et al* 1991, Nishikimi *et al* 1986, Selcuk *et al* 2007, Tsai *et al* 1990]. A large multi-centre study would provide more accurate estimates of the predictive value of BNP for clinical outcomes and more reliably determine the optimal cut-levels for intervention in combination with echocardiographic data. Patients with AF tended to have more severe MS, but associations between natriuretic peptides and other variables were similar for patients in AF and sinus rhythm (Figure 4.1). Valve morphology was excluded when evaluating ACC/AHA guideline criteria for PMBV.

Clinical decisions on treatment and timing of referral for mitral valvuloplasty or surgery were made by the patient's usual cardiologist, blinded to clinical, peptide and echocardiographic data collected for the study. The study included some symptomatic patients who were not referred for intervention on the judgment of their usual cardiologist because symptoms were difficult to evaluate or not limiting. Inclusion of an exercise test in all patients allowed an objective measure of exercise capacity in both symptomatic and asymptomatic patients at low risk. Subgroup analyses have limited statistical power but associations between BNP, exercise

capacity and left atrial area were similar for asymptomatic patients and the combined patient group.

4.7 CONCLUSION

BNP provides complementary information to clinical assessment of symptoms and echocardiography in MS, and may identify patients with reduced exercise capacity related to the valve stenosis. BNP may be useful for risk stratifying patients with MS, particularly when symptoms are equivocal or access to echocardiography is limited.

4.8 ACKNOWLEDGEMENTS

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CHAPTER FIVE

NATRIURETIC PEPTIDES IN MITRAL REGURGITATION

Park R, Kerr AJ, Sharma V, et al.
Elevated BNP and Right Heart Function in Mitral Regurgitation:
An Exercise Stress Echo study.
Heart, Lung and Circ June 2006; 15 239

Kerr AJ, Raffel OC, Whalley GA, et al.
Elevated B-type natriuretic peptide despite normal left ventricular function on rest and exercise stress echocardiography in mitral regurgitation.
Eur Heart J 2008;**29**(3):363-70.

5.1 SUMMARY

The objective of this study was to determine whether an elevated B-type natriuretic peptide (BNP) concentration predicts left ventricular (LV) contractile dysfunction on exercise stress echocardiography in patients with severe mitral regurgitation (MR). Thirty-three patients with moderate-to-severe or severe MR, LV ejection fraction ≥60 % and New York Heart Association Class I or II symptoms and 12 controls underwent resting and exercise stress echocardiography.

In 20 MR patients, BNP concentration was within the normal range (mean ± standard deviation, 26.6±9.3 pg/mL), and in 13 MR patients, BNP was >42 pg/mL (67.8±26.3 pg/mL). LV end-systolic volume index after exercise was lower in controls than patients with MR ($p < 0.0001$), but similar in MR patients with normal and elevated BNP, respectively (controls 9±4, MR 20±7 vs. 20± 9 cm^2/m^2, $p<0.05$). Pulmonary artery systolic pressure (PAP) after exercise was higher in MR patients with elevated BNP compared to MR patients with a normal BNP (70±20 vs. 48±11 mmHg, $p<0.0001$) and significantly higher than controls (38±11 mmHg). A two-fold increase in plasma BNP concentration was associated with an average increase in resting PAP of 7.6 (95% CI 2.9, 12.2) mmHg, an increase in post-exercise PAP of 14.4 (95% CI 9.0, 19.9) mmHg and increase in left atrial area index of 2.1 (95% CI 0.5, 3.8) cm^2/m^2. However, there was no significant association between the plasma concentration of BNP and any rest or post-exercise measure of LV systolic function ($r < 0.25$, $p>0.05$ for all).

These findings suggest that the plasma concentration of BNP may be within the normal range in patients with moderate-to-severe or severe MR despite significant increases in LV end-systolic volume. Increased plasma BNP concentrations are associated with pulmonary hypertension on exercise and left atrial enlargement even when LV systolic function on exercise stress echocardiography is normal.

5.2 INTRODUCTION

Severe MR exposes the left atrium to an increase in both pressure and volume of blood during cardiac systole. In addition the left ventricle is exposed to an increased volume of blood in diastole. Consequently in contrast to MS both the left atrium and left ventricle are exposed to varying degrees of pressure and volume overload. In very severe MR that has been allowed to persist without mitral valve surgery, pulmonary hypertension can develop exposing the right ventricle to increased pressure loads. Consequently there are multiple stimuli for natriuretic peptide release in patients with significant MR. Previous studies, have demonstrated that in patients with MR the plasma concentration of BNP is higher in symptomatic compared with asymptomatic patients [Sutton *et al* 2003]. Other studies have demonstrated that patients with MR in whom the plasma BNP concentration is elevated may be more likely to have adverse clinical events during follow-up [Detaint *et al* 2005].

5.2.1 MANAGEMENT OF PATIENTS WITH MR

Current guidelines recommend surgery in patients with severe mitral regurgitation who are symptomatic [Bonow *et al* 2006]. They also recommend surgery in asymptomatic patients when there are signs of LV dysfunction (EF <60 %) or significant LV dilatation (LV end systolic dimension >45 mm). Consequently the measurement of BNP in these patients is unlikely to be helpful as the indications for surgery are already clear. Potentially of more use would be the ability of natriuretic peptides to identify patients with early signs of LV dysfunction or aid in the management of patients in whom assessment of symptomatic status is difficult. In

addition it can difficult to assess LV function in the setting of severe mitral regurgitation as the large volume of blood flowing into the relatively low pressure left atrium results in a hyperdynamic LV and early signs of LV dysfunction can be missed. Failure to recognize the onset of LV dysfunction may predispose the patient to an increased risk of complications and a higher perioperative risk. More recently assessment of long axis function with tissue Doppler and the presence of contractile reserve on stress echocardiography have been shown to identify subtle LV impairment in severe mitral regurgitation [Agricola *et al* 2004, Haluska *et al* 2003, Leung *et al* 1996].

5.2.2 STUDY AIMS

The aims of this study are to assess the factors influencing the release of natriuretic peptides in patients with moderate to severe and severe MR with normal LV ejection fraction (LVEF >60%). A secondary aim is to determine whether elevated plasma BNP concentrations can identify MR patients who have signs of early LV dysfunction on comprehensive echocardiography performed at rest and immediately post exercise.

5.3 METHODS

Patients were recruited as outlined in Chapter 2. Specific inclusion and exclusion criteria for this sub study are outlined in Table 5.1. Exercise stress echocardiography was performed using treadmill exercise according to a standard Bruce protocol.

5.3.1 ECHOCARDIOGRAPHIC ASSESSMENT

Comprehensive Echocardiography was performed by an expert sonographer on modern echocardiographic machines according to established protocols both at rest and immediately post exercise as described in Chapter 2.

Table 5.1. Inclusion and exclusion criteria for MR patients

Inclusion Criteria	Exclusion Criteria
Moderate –Severe MR	Previous Myocardial Infarction
Severe MR	LV impairment (LVEF <60 %)
Age >18years	Angina
	Symptoms of Heart Failure (more than equivocal symptoms)
	Renal Disease (Creatinine >160 μmol/L)
	Respiratory Disease
	Other Valve Lesions (>mild)

5.3.2 ASSESSMENT OF MR SEVERITY

Specifically for this study additional assessment was performed to assess the severity of mitral regurgitation. Quantitative assessment MR severity was quantified using both the volumetric and proximal iso-velocity surface area (PISA) methods. This allowed calculation of both the regurgitant volume and estimation of the effective regurgitant orifice area (EROA). The regurgitant volume of both methods was averaged to give the mean regurgitant volume. MR severity was also assessed semi-quantitatively using the vena contracta width and the previously described MR score [Thomas *et al* 1999]. The MR score is calculated from visual assessment of MR jet

penetration, mitral continuous-wave Doppler characteristics, left atrial size, pulmonary venous flow pattern, tricuspid regurgitation velocity, and PISA radius [Enriquez-Sarano *et al* 1995].

5.3.3 SPECTRAL DOPPLER AND TISSUE DOPPLER

Early (E) and late (A) mitral inflow velocities were measured by pulsed-wave Doppler ultrasound with the sample volume placed at the mitral leaflet tips. Tissue Doppler imaging was performed at the medial mitral annulus from the apical four-chamber view, and the peak systolic (S') and diastolic (E') mitral annular velocities and E/E' measured [Ommen *et al* 2000].

5.3.4 ASSESSMENT OF RIGHT HEART

Agitated saline was injected intravenously to enhance the TR jet profile to allow assessment of right ventricular systolic pressure (RVSP) using continuous-wave Doppler both at rest and immediately post exercise [Himelman *et al* 1990]. Right atrial pressure was estimated as described in Chapter 2 and added to the estimated RVSP to allow estimation of pulmonary artery pressure. RV function was assessed using the fractional area change method as calculated by (RV end-diastolic area - RV end-systolic area)/RV end-diastolic area from the apical 4-chamber view. RV longitudinal function was assessed using the peak systolic tricuspid annular velocity (S').

5.4 RESULTS

33 patients with mitral regurgitation and 12 controls were recruited. Sixteen patients with MR were asymptomatic and 17 patients had mild or equivocal symptoms. The predominant aetiology of mitral regurgitation was mitral valve prolapse (26 patients) with the remainder (7 patients) having rheumatic mitral regurgitation.

5.4.1 COMPARISON OF ALL PATIENTS AND CONTROLS

The mean age for patients and controls was 53 and 51 years, respectively. There was a small but not significant excess of men in the MR group (55% vs. 33%, P=0.21).

5.4.2 COMPARISON OF MR WITH NORMAL BNP VS. CONTROLS

Baseline characteristics for controls and MR patients stratified by whether BNP remained within the normal range (<42 pg/mL) or was elevated (>42 pg/mL) are shown in Table 5.2. Although BNP remained within the normal range in 20 patients with MR, the actual plasma concentration of BNP was higher than that of age and sex matched controls. In addition these patients had significantly larger left ventricular volumes at rest than controls indicating that significant LV remodeling can occur while plasma BNP concentrations remain within the established normal range. In addition, mitral annular tissue velocities during both systole (S') and diastole (E'), and peak mitral E velocity were higher than in normal controls. MR patients with a normal BNP had resting pulmonary artery pressures marginally above the upper limits of normal but this was significantly higher than normal controls.

This difference was more marked with exercise and MR patients with a normal BNP had slightly lower exercise capacity.

Table 5.2. Comparison of normal controls, and patients with mitral regurgitation with a plasma level of BNP above compared with below the normal reference range

	Normal Controls	MR (BNP <42 pg/mL)	MR (BNP >42 pg/mL)	P value*	P value**
Number Of Subjects (n)	12	20	13	-	-
Age (years)	51 (14)	48 (15)	61 (16)	0.59	0.02
BNP (pg/mL)	17.6 (4.5)	26.7 (9.4)	68.0 (55.5)	0.004	<0.0001
ANP	41.6 (19.4)	82.5 (18.5)	162.9 (88)	<0.0001	<0.0004
NYHA Class >1	0 (0%)	9 (45%)	8 (62%)	-	-
Resting Echocardiography					
Regurgitant Volume (mL)	-	85 (34)	73 (32)	-	0.33
Vena Contracta (mm)	-	6.1 (1.0)	6.4 (1.2)	-	0.45
LAAI (mL/m^2)	10 (1.7)	17.1 (4.5)	18.1 (4.4)	<0.0001	0.46
PAP (mmHg)	22 (4)	32 (7)	46 (15)	0.01	0.0002
S' Tricuspid Annulus (cm/s)	12.3 (2.2)	14.3 (3.0)	13.8 (1.8)	0.03	0.60
RV Fractional Area Change	0.41 (0.07)	0.32 (0.09)	0.27 (0.07)	0.007	0.11
LV Function (rest)					
LVEDVI (mL/m^2)	46 (9)	77 (14)	75 (14)	<0.0001	0.7
LVESVI (mL/m^2)	16 (6)	27 (7)	26 (6)	<0.0001	0.53
LVIDs (cm)	3.2 (0.6)	3.3 (0.5)	3.4 (0.6)	0.72	0.64
LV Ejection Fraction (%)	66 (8)	64 (7)	65 (7)	0.31	0.62
E Wave (m/s)	0.7 (0.2)	1.1 (0.3)	1.2 (0.4)	0.0001	0.36
S' Mitral Annulus (cm/s)	8.3 (1.7)	8.7 (1.7)	9.0 (1.7)	0.51	0.61
E' Mitral Annulus (cm/s)	9.4 (3.5)	10.4 (3.0)	10.0 (2.5)	0.4	0.7
E/E' Mitral Annulus	7.7 (1.7)	11.7 (4.5)	13.4 (4.6)	0.0002	0.39
Stress Echocardiography					
PAP (mmHg)	38 (8.2)	48 (11)	70 (20)	0.01	0.0002
LVEDVI (mL/m^2)	38 (9.0)	65 (17)	59 (17)	<0.0001	0.25
LVESVI (mL/m^2)	8.5 (3.9)	20 (7)	20 (9)	<0.0001	0.91
LVEF (%)	78 (8.5)	70 (6)	66 (9)	0.005	0.16
EF (post–pre exercise)	11.6 (4.7)	5.7 (8.2)	0.5 (9.6)	0.05	0.07
Treadmill Exercise					
Exercise Time (min)	10.7 (2.9)	8.9 (2.0)	5.8 (2.2)	0.04	0.0006
Peak SBP (mmHg)	159 (24)	158 (28)	130 (28)	0.22	0.04
Increase In SBP (mmHg)	47 (14)	37 (16)	23 (20)	0.12	0.04
Peak Heart Rate (bpm)	164 (10)	150 (20)	131 (20)	0.48	0.02

*p value for MR patients normal BNP (≤42pg/mL) vs. controls;

** p value MR patients normal (≤42pg/mL) vs. elevated BNP(>42pg/mL)

5.4.3 COMPARISON OF MR PATIENTS WITH ELEVATED VS. NORMAL BNP

In this cohort, MR patients with an elevated plasma concentration of BNP tended to be slightly older and had reduced exercise capacity than those with a normal BNP. In addition they had higher pulmonary artery pressure both at rest and with exercise. There were no statistically significant differences in any resting markers of LV function between patients with an elevated BNP compared to those with a normal BNP. There was a trend towards lower augmentation of LVEF with exercise in the patients with elevated BNP (increase in EF=5.7% vs. 0.5%, p=0.07), but after adjustment for age and beta-blocker status this was not significant (p=0.49). All other results were similar after adjusting for age and beta-blocker status.

5.4.4 COMPARISON OF ASYMPTOMATIC VS. SYMPTOMATIC PATIENTS

For patients with NYHA Class 2 symptoms compared with asymptomatic patients with MR, the plasma concentration of BNP was higher (51.9 vs. 33.2 pg/mL, p= 0.02), rest PAP was greater (42 vs. 32 mmHg, $P < 0.0001$) and exercise duration was less (5.9 vs. 9.6 min, $p < 0.0001$). However, there were no differences in any resting or post-exercise measure of LV function between symptomatic and asymptomatic patients with MR.

5.4.5 ASSOCIATIONS BETWEEN BNP AND STRESS ECHOCARDIOGRAPHY

For MR patients, associations between different echocardiographic measures at rest and after exercise, with both the plasma concentrations of BNP and exercise capacity are presented in Table 5.3. There were strong correlations between the plasma

concentration of BNP and PAP both at rest and after exercise (Figure 5.1). There were also moderate correlations between the plasma concentration of BNP and septal E/E', left atrial area index, and an inverse correlation with treadmill exercise capacity (Figure 5.2). In contrast, there was no correlation between the plasma concentration of BNP and any resting or post-exercise measurement of LV function, including LVEF, indexed LV volumes or change in EF after exercise (Figure 5.3). There was also no association between the plasma concentration of BNP and any echocardiographic measures of severity of MR or RV function assessed using tricuspid annular tissue velocities and change in RV fractional area at rest

The echocardiographic measures most strongly associated with treadmill exercise capacity were resting and post-exercise pulmonary pressure. There was a weak association between exercise capacity and post-exercise LV end-diastolic volume index but no clear association with other resting or post-exercise measures of LV function.

After adjusting for age and sex, the association between natural log scaled BNP and both post-exercise pulmonary artery pressure (partial r^2=0.49, p<0.0001) and resting pulmonary artery pressure (partial r^2=0.30, p=0.001) remained strong. There was a more modest association between BNP and with exercise capacity (partial r^2=0.21, p=0.01) and with left atrial area index (partial r^2=0.16, p=0.02). The association of BNP with resting septal E/E' (partial r^2=0.16, p=0.04) was of borderline statistical significance. A two-fold increase in plasma BNP was associated with an average increase in resting PAP of 7.6 (95% CI 2.9, 12.2) mmHg, an increase in post-exercise

PAP of 14.4 (95% CI 9.0, 19.9) mmHg and 2.1 (95% CI 0.5, 3.8) cm^2/ m^2 increase in left atrial area index.

Figure 5.1. Association between the natural log of B-type natriuretic peptide (LnBNP) and exercise capacity measured in minutes on the Bruce protocol for normal controls (open squares) and patients with severe mitral regurgitation (closed circles). The non-transformed values of B-type natriuretic peptide in pmol/L are shown in brackets. There is an inverse correlation between exercise capacity and natural log of B-type natriuretic peptide (r=-0.6, p=0.0002) for patients with mitral regurgitation.

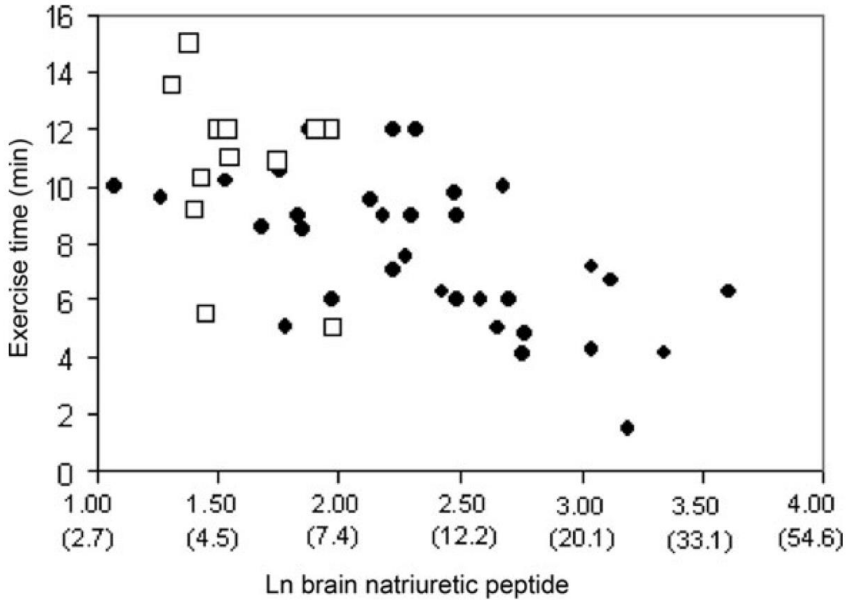
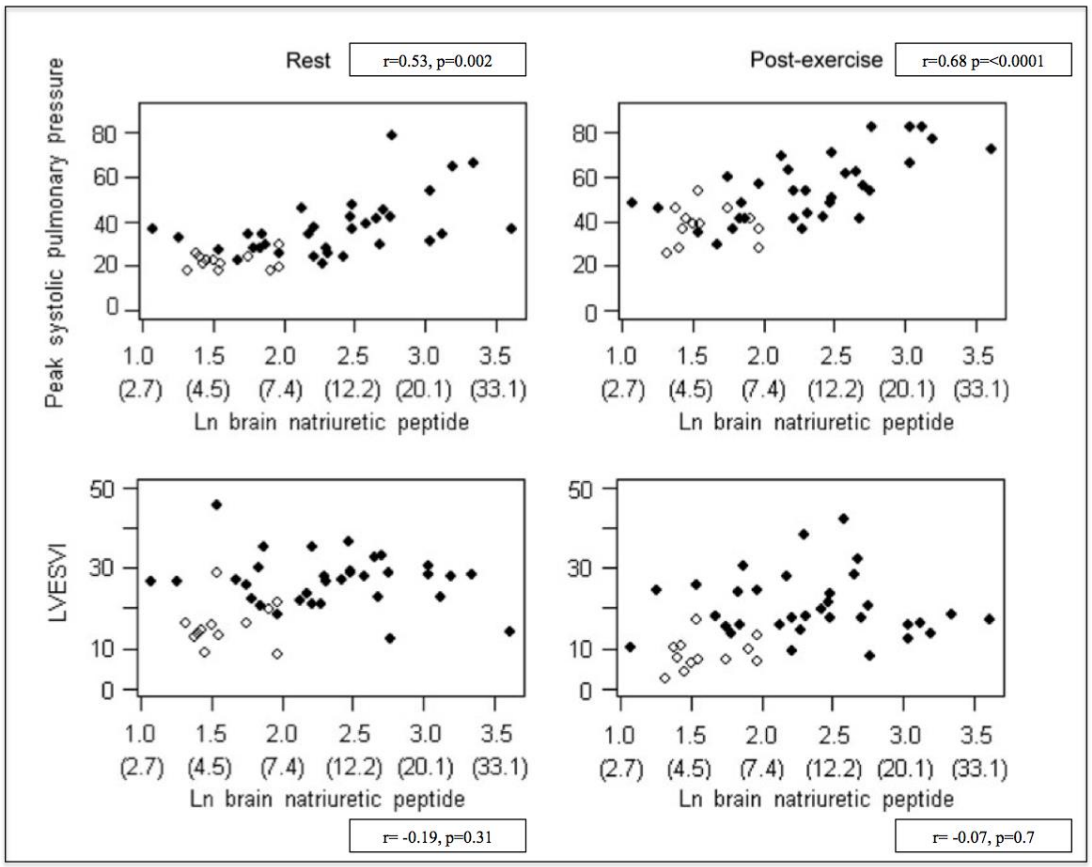


Table 5.3. Correlations (r) between the plasma level of B type natriuretic peptide and exercise capacity with resting and post-exercise echocardiographic measurements for mitral regurgitation patients

	Correlation With BNP		**Correlation With Exercise Capacity**	
	r	p	r	p
Rest Echocardiography				
Regurgitant Volume	-0.20	0.27	0.21	0.25
Left Atrial Area Index	0.42	0.02	0.03	0.86
Pulmonary Artery Pressure	0.53	0.002	-0.42	0.01
LVEDVI	-0.02	0.28	0.27	0.13
LVESVI	-0.19	0.31	0.14	0.43
LV Ejection Fraction	0.23	0.93	-0.003	0.99
S' Septal	-0.09	0.63	-0.04	0.85
E Wave	0.25	0.15	-0.22	0.22
E' Septal	-0.24	0.21	0.29	0.13
E/E' Septal	0.41	0.03	-0.27	0.17
Stress Echocardiography				
Pulmonary Artery Pressure	0.68	<0.0001	-0.50	0.003
LVEDVI	-0.21	0.23	0.42	0.02
LVESVI	-0.07	0.70	0.24	0.18
LV Ejection Fraction	-0.12	0.56	0.12	0.51
EF (post-pre exercise)	-0.31	0.07	0.21	0.24
Exercise Time	-0.60	0.0002	-	-

Figure 5.2. Association between the natural logarithm (Ln) of B-type natriuretic peptide and pulmonary pressure (upper panels), and left ventricular end-systolic volume index (LVESVI) (lower panels) for normal controls (open symbols) and patients with mitral regurgitation (closed symbols). The values of non-transformed values of B-type natriuretic peptide in pmol/L are shown in brackets.



5.4.6 PREDICTIVE ACCURACY OF BNP IN IDENTIFYING SIGNIFICANT MR

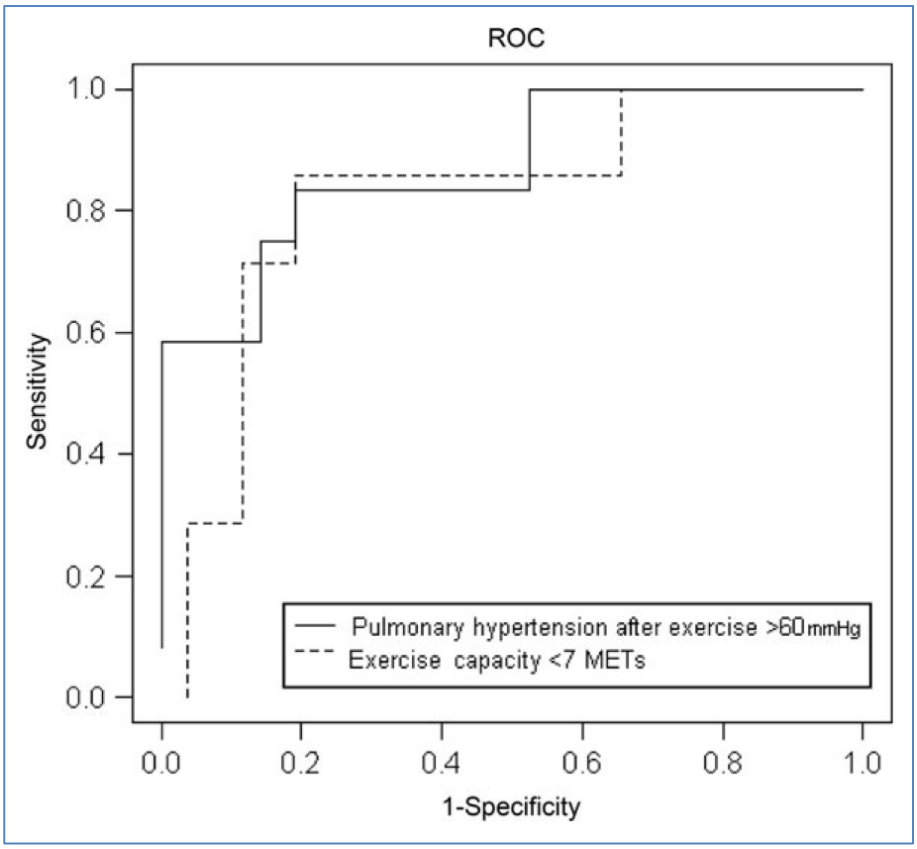
The sensitivity and specificity of BNP for predicting guideline based abnormal resting and post-exercise pulmonary pressures thresholds [Bonow *et al* 2006], and impaired exercise capacity [Thompson *et al* 2000] are presented in Table 5.4 and Figure 5.3. BNP above the upper limit of normal was a good predictor of PAP>60 mmHg after exercise and PAP >50 mmHg at rest, and a weaker predictor of reduced exercise capacity defined as a failure to complete 6 minutes of the Bruce Protocol (equivalent to <7METs)

Table 5.4. Sensitivity, specificity and AUC for B-type natriuretic peptide for pulmonary hypertension and exercise capacity

	Number Of Subjects	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC (95% CI)	P value
Pulmonary Pressure					
Rest (>50 mmHg)	4	100 (40, 100)	69 (49, 85)	0.93 (0.84, 1.0)	0.03
Post Exercise (>60 mmHg)	12	75 (43, 95)	81 (58, 95)	0.87 (0.75, 1.0)	0.005
Impaired Exercise Capacity					
METs Achieved <7	7	86 (42,100)	73 (52, 88)	0.82 (0.64, 1.0)	0.03

METs: metabolic equivalents; CI: confidence interval; AUC: area under the curve

Figure 5.3. Receiver operating characteristics curve for B-type natriuretic peptide for pulmonary hypertension after exercise >60 mmHg, and exercise capacity <7 metabolic equivalents (METs)



The sensitivity and specificity of B-type natriuretic peptide >42 pg/mL (upper reference limit for laboratory) for these outcomes are presented in Table 5.4.

5.5 DISCUSSION

5.5.1 MAIN FINDINGS

In this study of asymptomatic or mildly symptomatic patients with moderate to severe or severe MR and preserved LVEF at rest, a higher plasma concentration of BNP was associated with higher pulmonary pressures, (both at rest and immediately post exercise), increased left atrial volume and lower exercise capacity on functional testing. However, there were no clear associations between BNP and any measures of LV function at rest or after exercise. These results suggest that an increase in the plasma BNP concentration does not necessarily indicate the presence of early or 'latent' LV dysfunction in patients with severe MR.

5.5.2 BNP AND MEASURES OF LV FUNCTION

The lack of a clear association between plasma levels of BNP and measures of LV function in the current study contrasts with some previous reports [Detaint *et al* 2005, Detaint *et al* 2006, Yusoff *et al* 2006]. In a large cohort study including NYHA Class 1–4 patients and mild to severe organic MR, Detaint found a weak but statistically significant association between the plasma concentration of BNP and LV end-systolic volume index (r=0.26). In a separate report that included subjects with both organic and functional MR, Detaint et al [Detaint *et al* 2006] reported that LV end-systolic volume index was the major determinant of the plasma concentration of BNP. However, in this study, most patients with a LV end-systolic volume ≥60 mL/m^2 and an elevated plasma BNP concentration had primary LV dysfunction.

Yusoff et al [Yusoff *et al* 2006] also reported statistically significant associations between the plasma concentration of N-terminal-BNP and several measures of LV remodelling including the LV sphericity index and LV end-systolic volume in 38 patients with severe MR and an EF >55 %. However, unlike our study, the majority of patients had NYHA Class 2 or 3 symptoms and some patients had very high plasma concentrations of N-terminal-BNP. The variable association between BNP and LVESVI observed in these studies probably reflects different inclusion criteria.

In the current study, the plasma concentration of BNP remained within the normal range for many MR patients despite significant increases in LV volumes. This suggests that compensatory changes in LV volume with MR are not necessarily associated with an increase in the plasma concentration of BNP above the normal range. Increase in E/E' is associated with higher LV end-diastolic pressure in patients with impaired LV function [Nagueh *et al* 1997], and there was a modest association between E/E' and BNP in the current study. However in severe MR, MV E increases due to the large volume of blood passing through the MV in diastole and in these patients the LV end-diastolic pressure may be normal even if MV E is high. Consequently the relationship between LV end-diastolic pressure and E/E' may be different in patients with significant MR.

5.5.3 BNP AND MEASURES OF LEFT ATRIAL STRETCH

Natriuretic peptides are usually produced by ventricular myocytes in response to increases in wall stress and by atrial myocytes in response to increased atrial wall stress [Goetze *et al* 2006]. In MR, the predominant pressure load is on the left atrium

and, if pulmonary hypertension is present on the RV. In the current study, the plasma concentration of BNP was not clearly associated with any measures of early dysfunction. These observations are consistent with increased BNP production by the left atrium in response to the chronic increase in left atrial wall stress. Limited evidence suggests increased synthesis of BNP by atrial myocytes in response to chronic increases in wall stress [Langenickel *et al* 2000] and co-storage of BNP with ANP in atrial granules [Goetze *et al* 2006]. The strong association between the plasma concentration of BNP and pulmonary artery pressure also raises the possibility of increased BNP secretion from the RV. However, in the current study, there was no association between the plasma concentration of BNP and measures of resting RV function.

5.5.4 BNP, SYMPTOMS AND EXERCISE CAPACITY

Previous studies of organic MR have reported an association between the presence and severity of symptoms and an increase in plasma concentrations of BNP [Detaint *et al* 2005, Sutton *et al* 2003, Yusoff *et al* 2006]. These observations are consistent with the strong correlation between BNP and functional capacity in the current study ($r=0.6$, $p<0.0001$) and with maximum oxygen consumption in a previous study of severe organic MR [Messika-Zeitoun *et al* 2006]. However, resting and exercise stress measures of LV function were weak predictors of exercise capacity in this study and of maximum oxygen consumption in previous studies of severe MR [Messika-Zeitoun *et al* 2006, Yusoff *et al* 2006]. Pulmonary artery pressure was the strongest echocardiographic predictor of functional capacity in the current study. These observations are consistent with severe MR leading to an increase in LA

pressure and pulmonary hypertension during exercise even when LV contractility is normal or increased. The novel observation from the current study is that these effects of severe MR are associated with an increase in the plasma concentration of BNP.

5.5.5 CLINICAL IMPLICATIONS

In patients with a LVEF >60 %, the presence of symptoms attributable to MR, pulmonary hypertension at rest and/or after exercise, and decreased exercise capacity are ACC/AHA and European Society of Cardiology (ESC) Class I or IIa indications for mitral valve surgery [Bonow *et al* 2006, Vahanian *et al* 2007]. Measuring the plasma concentration of BNP may therefore be useful for evaluating asymptomatic patients, and those with equivocal symptoms, even though an increase in BNP does not necessarily indicate the onset of LV dysfunction. Further studies are needed to reliably assess the value of BNP for this purpose.

5.5.6 STUDY LIMITATIONS

A limitation of this study is that it does not include follow-up for clinical outcomes or reassessment of LV function after mitral surgery. We are therefore unable to determine which patients, if any, would develop LV dysfunction. However the presence of latent LV dysfunction was assessed using resting and post-exercise measures of LV size and performance as previously described [Leung *et al* 1996]. Decrease in the peak systolic mitral annular velocity is also associated with a lower LVEF after surgery and with decreased contractile reserve on exercise stress echocardiography [Agricola *et al* 2004]. However, there was no evidence for an

association between the plasma concentration of BNP and this measure in the current study. The peak systolic mitral annular velocity after exercise may be a more sensitive measure of early LV dysfunction [Haluska *et al* 2003, Van Pelt *et al* 2007] but was not measured in the current study.

This study was limited to a subset of patients with clinically important MR in whom indications for surgery were at most equivocal. As discussed previously, we excluded patients with Class III or IV symptoms or LV impairment. Prior studies suggest a relationship between BNP and LV dilatation and dysfunction when such patients are included. The primary focus of this study was to assess the relationship of BNP to exercise LV parameters and pulmonary pressures. Because we used treadmill exercise there was a limited time window on cessation of exercise to obtain echo data and we were therefore unable to assess other variables of interest including exercise RV function and change in MR severity with exercise. Although the relationship between BNP and both pulmonary pressures and exercise capacity are statistically robust, the predictive value of BNP for individual patients requires further study in a larger cohort.

5.6 CONCLUSION

In this study, many patients with moderate-to-severe or severe MR and a resting EF >60 % had significant increases in LV end-systolic volumes, despite plasma BNP concentrations within the normal range. Elevated BNP predicted the presence of

pulmonary hypertension and left atrial enlargement even when LV systolic function was normal at rest and on stress echocardiography.

5.7 ACKNOWLEDGMENTS

We are very grateful to Dr Gillian Whalley for her assistance with left ventricular analysis, to Jenny White for coordinating the study and to Margaret Oldfield for her expert echocardiography. This research was supported by grants from the New Zealand Heart Foundation, Middlemore Hospital Cardiac Trust (Dr Sharma) and Green Lane Research and Education Fund (Dr Stewart).

CHAPTER SIX

NATRIURETIC PEPTIDES IN AORTIC REGURGITATION

Gabriel RS, Kerr AJ, Sharma V *et al*.
B-Type natriuretic peptide and left ventricular dysfunction on exercise echocardiography in patients with chronic aortic regurgitation.
Heart. 2008 Jul; 94(7): 897-902.

6.1 SUMMARY

The aim of this study was to determine whether plasma concentrations of B-type natriuretic peptide (BNP) predict left ventricular (LV) dysfunction on exercise echocardiography in patients with moderate to severe aortic regurgitation (AR).

Thirty-nine asymptomatic or mildly symptomatic patients with chronic moderate to severe AR and a normal LV ejection fraction (>50%), and 10 normal controls underwent sampling of natriuretic peptides immediately before exercise stress echocardiography.

We found that LV end systolic volume index (LVESVI) was increased in AR patients with normal BNP (≤42 pg/mL) compared with controls (mean±SD 32±13 vs 17±7 mL/m^2, p=0.002) but was similar for AR patients with normal and elevated BNP (38±16, p=0.14). In AR patients there was no association between plasma BNP and any measure of LV function on echocardiography at rest ($r<0.30$, $p>0.05$ for all). However, there was a modest but statistically significant association between the plasma concentration of BNP and severity of AR indicated by a greater AR:LV outflow tract width ratio (r=0.37, p=0.02) and lower diastolic blood pressure (r=-0.44, p=0.004). Increased BNP was also associated with a greater LVESVI (r=0.33, p=0.04) and lower LV longitudinal strain rate (r = -0.037, p=0.02) on echocardiography after exercise.

In moderate to severe AR compensatory LV remodelling can occur with no increase in plasma BNP. Increased BNP is associated with more severe regurgitation and changes consistent with early LV dysfunction on exercise echocardiography.

6.2 INTRODUCTION

Asymptomatic patients with chronic aortic regurgitation (AR) can remain clinically stable for years, but many eventually develop symptoms or LV dysfunction. The presence of symptoms, decreased LV function (LVEF <50 %) or severe LV dilatation (LV end systolic dimension of 50-55 mm) predicts poorer outcome and hence these findings are all an indication for consideration of surgery according to current guidelines [Bonow *et al* 2006, Vahanian *et al* 2007]. However, up to a quarter of asymptomatic patients with chronic AR develop LV dysfunction without recognised symptoms [Vahanian *et al* 2007]. Furthermore the onset of early symptoms can be difficult to evaluate clinically. This is important as even mildly symptomatic patients (NYHA 2) have a mortality of approximately 6.4% per year if untreated [Klodas *et al* 1997]. In addition many patients can develop significant LV dilatation and/or mild LV dysfunction without becoming symptomatic [Vahanian *et al* 2007]. Consequently it would be valuable if other methods can identify asymptomatic patients at risk of early decompensation in moderate to severe AR.

6.2.1 PLASMA BNP CONCENTRATIONS IN AORTIC REGURGITATION

Previous studies have suggested that in patients with AR, BNP concentrations fall after aortic valve replacement but continue to rise in those patients treated conservatively [Weber *et al* 2005]. In addition in another study, plasma BNP concentrations were higher in patients with AR who were symptomatic [Gerber *et al* 2003]. However there was no association between BNP and any marker of increasing

LV volume or ejection fraction on echocardiography at rest. In addition although several studies have suggested that exercise stress echocardiography can be used to identify subtle LV dysfunction in patients with chronic AR [Borer *et al* 1998, Dehmer *et al* 1981, Johnson *et al* 1983, Schuler *et al* 1982, Thompson *et al* 1985], no previous studies have included data from exercise stress echocardiography to determine whether plasma natriuretic peptide concentrations can be identify patients with early LV dysfunction.

6.2.2 STUDY AIMS

The aims of this sub-study where to assess the relationship of plasma BNP concentrations with markers of disease severity and to determine whether BNP could identify patients with early LV dysfunction either at rest or with exercise in patients who where either asymptomatic or had equivocal symptoms.

6.3 METHODS

6.3.1 STUDY POPULATION

The patients were recruited according to the general methodological criteria described in Chapter 2. Specifically for this study consecutive patients with moderate-to-severe or severe aortic regurgitation attending outpatient clinics in the Auckland Region were invited to participate. This was defined according to the ASE criteria (AR jet: Left Ventricular Outflow Tract (LVOT) width ratio was >0.3 and

holo-diastolic flow reversal in the descending thoracic aorta) [Zoghbi *et al* 2003]. Key inclusion and exclusion criteria are as defined in Table 6.1.

Table 6.1: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Moderate –Severe AR*	Previous Myocardial Infarction
Severe AR	LV Impairment (LVEF <50 %)
Age >18years	Significant Aortic Dilatation (>5 cm)
	Atrial Fibrillation
	Renal Disease (Creatinine >160 µmol/L)
	Respiratory Disease
	Other Valve Lesions (>mild)

*AR jet: Left Ventricular Outflow Tract (LVOT) width ratio was >0.3 and holo-diastolic flow reversal in the descending thoracic aorta

6.3.2 CLINICAL ASSESSMENT

Subject details were collected from standardised questionnaires by the study cardiologist at the time of enrolment. A baseline medical history, medication regime, weight, height, pulse and supine blood pressure were obtained. The symptomatic status of each patient was graded according to the NYHA classification system. An ECG was obtained and baseline blood tests for natriuretic peptide levels were taken.

6.3.3 MEASUREMENT OF NATRIURETIC PEPTIDES

Plasma concentrations of BNP were obtained as outlined in Chapter 2

6.3.4 EXERCISE TESTING

All subjects underwent a symptom-limited exercise test using an adaptation of the standard Bruce protocol as defined in Chapter 2. The speed and or incline of the treadmill increased at 1-min intervals but the overall workload at the end of each stage was the same as for the Bruce protocol. The test was terminated if the patient developed marked dyspnoea, fatigue, chest discomfort, >2 mm ST depression, significant arrhythmia, or at patient request.

6.3.5 REST AND STRESS ECHOCARDIOGRAPHY

Two-dimensional echocardiography was performed using a Vivid 7 Dimension machine (General Electric, Vingmed Ultrasound, Horten, Norway) before and immediately after exercise treadmill testing as outlined in Chapter 2. The acquisition protocol is outlined in Appendix 2.

6.3.6 ASSESSMENT OF AR SEVERITY

LV mass was calculated from linear dimensions using the American Society of Echocardiography recommended formula [Lang *et al* 2005]. AR severity was assessed according to standard criteria. This included measurement of the AR jet:

LVOT width ratio from the parasternal long axis view and the AR jet: LVOT area. The AR pressure half time, peak diastolic and end-diastolic flow velocities in both the descending thoracic and abdominal aorta were made.

6.3.7 SPECKLE TRACKING

In order to detect more subtle abnormalities of LV dysfunction, standard long and short axis LV images were acquired at high frame rates to allow measurement of strain, strain rate and LV rotation. Endocardial borders were traced in apical and short axis views and commercial software automatically tracked myocardial motion in six regions of interest. Global LV longitudinal strain and strain rate was generated by averaging measurements from all regions of interest in the apical four-chamber view [Cho *et al* 2006]. LV torsion measurements were made using a previously described technique [Notomi *et al* 2005].

6.3.8 EXERCISE ECHOCARDIOGRAPHY

Immediately following peak exercise, echocardiographic images were obtained as outlined in appendix 2. Apical four-chamber views were obtained at high frame rates for LV volume calculations, pulsed wave tissue Doppler imaging and 2D speckle tracking based LV longitudinal strain and strain rate measurements. LV torsion measurements could not be reliably obtained after exercise.

6.3.9 STATISTICAL ANALYSIS

Correlation coefficients were used to evaluate associations between continuous variables. Chi-squared tests were used to investigate whether the proportion of NYHA class and AR severity grade differed across groups. Fisher exact tests were used where appropriate. Mann–Whitney U tests were applied to test whether the AR severity measures and exercise echocardiography differed between groups. Analyses of covariance were used to compare across normal control and AR patients with normal and elevated BNP adjusting for age; F test and contrasts were derived for pairwise comparisons. Post hoc Tukey studentised range significant tests (HSD) were also applied in the multi-group comparisons. Peptide concentrations underwent natural log transformation due to their right skew distribution in all analyses. Results are presented as means and standard deviations unless otherwise stated. A p value <0.05 was considered statistically significant. SAS institute released SAS 9.1 was used in the analysis.

6.4 RESULTS

Thirty-nine patients with AR and ten age and sex-matched control subjects were recruited. The underlying aetiology of aortic regurgitation was rheumatic heart disease (18), bicuspid aortic valve (15), connective tissue disease (one), aortic root dilatation (two) and uncertain (two). The baseline characteristics are shown in Table 6.2 The patients had a mean age of 42 years (range 18 to 71). The majority (32) of patients were asymptomatic with 7 patients having equivocal symptoms. Twenty-five

(64%) AR patients were on an angiotensin converting enzyme inhibitor, five (13%) a calcium channel blocker, and two (5%) a B-blocker. No control patients were taking medication.

6.4.1 COMPARISON OF AR PATIENTS WITH CONTROLS

Compared to controls, AR patients had higher systolic BP and lower diastolic blood pressures at rest. AR patients also had a higher body mass index. Body surface area was similar in AR patients and control subjects (1.9±0.3 vs 2.1±0.2 m^2, p=0.6). BNP concentrations were not significantly higher in AR patients compared to controls (34 IQR (23/43) vs 33 IQR 29-36 pg/mL; p=0.94)

6.4.2 COMPARISON OF PATIENT WITH NORMAL VS RAISED BNP

Patients with AR were divided into two groups according to whether they had normal (≤42 pg/mL) or elevated BNP (>42 pg/mL) concentrations as determined by the normal reference range for the assay used [Yandle *et al* 1993]. Clinical and echocardiographic data are compared for normal controls and patients with AR by plasma BNP in Table 6.3. Associations between the plasma concentration of BNP and echocardiographic measurements at rest and after exercise are presented in Table 6.4.

Table 6.2. Baseline characteristics of patients and controls

	Controls (n=10)	**AR Patients (n=39)**	**P value**
Age (median, range)	42 (42-63)	42 (18-71)	
Female	4 (40%)	6 (15%)	
NYHA>1	0	7 (18%)	-
Medication			
ACE Inhibitor	0	25 (64%)	-
CCB	0	5 (13%)	-
B-Blocker	0	2 (5%)	-
Systolic BP (mmHg)	112 (9)	129 (6)	0.004
Diastolic BP (mmHg)	71 (6)	58 (13)	0.01
BMI (kg/m2)	24 (3)	29 (5)	0.01

NYHA: New York Heart Association; ACE: angiotensin converting enzyme; CCB: calcium channel blocker; BP: blood pressure, BMI: body mass index

Table 6.3. Exercise stress echo data for patients and controls

	Controls (n=10)	**AR (BNP≤ 42 pg/mL) (n-28)**	**AR (BNP> 42pg/mL) (n=11)**	**P value***	**P value****
Age In Years (median, range)	42 (24-63)	41 (18–68)	47 (20–71)	0.95	0.6
BNP (pg/mL)	33 (27, 36)	28 (21, 36)	64 (59, 133)	0.13	<0.001
NYHA class >1	0 (0%)	3 (11%)	4 (36%)	0.55	0.06
Echocardiography					
Severe Regurgitation*		4 (14%)	6 (55%)		0.02
AR Jet to LVOT Width Ratio		0.5 (0.13)	0.62 (0.16)		0.03
DA Peak Velocity Diastole (m/s)		0.55 (0.15)	0.74 (0.26)		0.02
DA End-diastolic Velocity (m/s)		0.22 (0.1)	0.3 (0.15)		0.04
LA Area Index (cm^2/m^2)	9.8 (2.1)	10.4 (1.7)	11.9 (2.3)	0.35	0.02
Estimated PAP (mmHg)	25 (4)	27 (6)	32 (6)	0.49	0.03
LV Function (rest)					
LVEDVI (mL/m^2)	51.3 (13.5)	88.7 (27.8)	97.6 (30.5)	<0.001	0.29
LVESVI (mL/m^2)	17.1 (7.1	32.4 (13.2)	37.6 (16.2)	0.001	0.35
LV Ejection Fraction (%)	68 (7)	64 (6)	63 (6)	0.43	0.62
LVIDd (cm)	4.7 (0.5)	5.9 (0.7)	5.9 (0.7)	<0.001	0.96
LVIDs (cm)	3.1 (0.7)	4 (0.5)	4.3 (0.9)	0.001	0.56
LV Mass Index (g/m^2)	89 (21)	175 (43)	201 (38)	<0.001	0.08
S' Mitral Annulus (cm/s)	11.6 (2.3)	8.1 (2.1)	8.1 (1.8)	0.002	0.65
E' Mitral Annulus (cm/s)	9.7 (1.5)	8.3 (1.2)	8.5 (1.3)	0.001	0.69
E/E' Mitral Annulus	6.9 (1.7)	9.7 (2.6)	9.4 (2.3)	0.005	0.82
Treadmill exercise					
METS Achieved	14.6 (2.1)	11 (3.3)	10.7 (4)	0.01	0.78
Peak Systolic BP (mmHg)	159 (11)	187 (24)	191 (25)	0.002	0.66
Peak HR (beats/min)	173 (10)	159 (17)	148 (18)	0.01	0.11
LV Function (exercise)					
LVEDVI (mL/m^2)	37.8 (12.6)	57.8 (18.3)	76.6 (30.5)	<0.001	0.05
% Change In LVEDVI	-26 (18)	-34 (13)	-22 (14)	0.16	0.05
LVESVI (mL/m^2)	7.3 (4.2)	17.4 (8.4)	28.8 (19.6)	0.001	0.09
% Change In LVESVI	-58 (17)	-46 (17)	-26 (29)	0.08	0.03
LVEF (%)	82 (7)	71 (8)	66 (11)	0.002	0.25
Change In EF (%)	14 (6)	6 (7)	2 (11)	0.008	0.18
S' Mitral Annulus (cm/s)	22 (4)	15 (4)	13 (4)	<0.001	0.3
Change In S' Septum (cm/s)	11 (4)	7 (4)	5 (4)	0.03	0.24

*p value AR patients normal BNP vs. controls. ** p value, AR patient normal BNP vs. AR patients elevated BNP

Table 6.4. Correlation (r) between the plasma concentration of (the natural logarithm (Ln) of BNP and clinical and echocardiographic measures

	Ln BNP	
	r	p
AR severity		
Diastolic BP (mmHg)	-0.45	0.004
AR jet to LVOT width ratio	0.37	0.02
AR jet to LVOT area ratio	0.43	0.007
Echocardiography (rest)		
LVEDVI (mL/m^2)	0.16	0.34
LVESVI (mL/m^2)	0.19	0.24
LV Ejection Fraction (%)	-0.11	0.50
LV Mass Index (g/m^2)	0.28	0.08
S' Mitral Annulus (cm/sec)	-0.002	0.99
Longitudinal Strain Rate (/s)	-0.19	0.25
LV Systolic Torsion (°)	0.15	0.38
Pulmonary Artery Pressure (mmHg)	0.39	0.02
LA Area Index (cm^2/m^2)	0.53	0.001
Treadmill exercise		
METS Achieved	-0.11	0.52
LV Function After Exercise		
LVEDVI (mL/m^2)	0.37	0.02
LVESVI (mL/m^2)	0.33	0.04
S' Mitral Annulus (m/s)	-0.28	0.09
Change In S' (m/s)	-0.27	0.10
Longitudinal Strain Rate (1/s)	0.33	0.04
Change In Longitudinal Strain Rate (1/sec)	-0.37	0.02

6.4.3 BNP AND ECHOCARDIOGRAPHIC VARIABLES AT REST.

There were significant associations between plasma concentrations of BNP and echocardiographic markers of severity of AR including diastolic blood pressure (r=-0.45, p=0.004), AR jet to LVOT width ratio (r=0.37, p=0.02) and AR jet to LVOT area ratio (r=0.43, p=0.007). However there were no associations between the plasma concentration of BNP and any markers of LV size or function at rest (Table 6.4).

Similarly when AR patients were stratified according to whether their BNP concentration was within the normal range or elevated, AR patients with an elevated BNP tended to have more severe aortic regurgitation but no significant difference were found in LV size or function (Table 6.3).

Despite no significant associations being found between BNP and resting markers of LV size and function, there were significant associations between the plasma concentration of BNP and LA area index (r=0.53; p=0.001) and a modest association with pulmonary artery pressure at rest (r=0.39; p=0.02).

6.4.4 BNP AND EXERCISE STRESS ECHO VARIABLES.

Despite only a small number of patients with mild or equivocal symptoms, AR patients had a lower exercise capacity than age and sex matched controls. This was the case both for AR patients in whom the plasma concentration of BNP remained within the normal range and those AR patients in whom BNP was elevated. However there was no significant difference in exercise capacity AR patients with

normal and elevated levels of BNP (11.0±3.3 vs. 10.7± 4.0 METs, p=0.78). However AR patients with BNP concentration >42 pg/mL had a tendency towards being more symptomatic than patients with BNP <42 pg/mL (36% versus 11%, p=0.06).

6.4.5 BNP AND LV FUNCTION ON ECHOCARDIOGRAPHY AFTER EXERCISE

Although no difference in resting LV size or function was noted, patients with a plasma BNP concentration >42 pg/mL tended to have larger left ventricle end diastolic (77±31 vs. 58±18 mL/m^2; p=0.05), larger end-systolic volumes (29±20 vs. 17±8 mL/m^2; p=0.09) and a smaller percentage decrease in LVESVI post exercise (-26±29 vs. -46±7 %; p=0.03). After adjustment for age this difference was statistically stronger with a p value of <0.01 for post-exercise LVESVI, % change in LVESVI, post exercise LVEDVI, and % change in LVEDVI. All other results were similar with and without adjustment for age. A lower longitudinal global strain rate (p=0.05) and change in strain rate (p=0.02) were also seen after exercise.

6.5 DISCUSSION

This study demonstrates a number of important findings in relation to the use of BNP in the assessment of patients with aortic regurgitation. Firstly many AR patients had significant LV remodelling despite a BNP that remained well within the normal range. This supports the findings from a previous study by Gerber et al [Gerber *et al* 2003] who investigated the role of BNP in patients with severe AR many of whom

had met the echocardiographic criteria for surgery. Again they found no significant association between plasma concentrations of BNP and any markers of LV size at rest. It is recognized that patients who undergo valve surgery after their left ventricle has become severely dilated are at an increased risk of complications and that in some cases the ventricles do not return to their normal size after surgery. Our study suggests that the finding of a normal plasma concentration of BNP cannot be reliably used to exclude the presence of significant LV dilatation in AR.

The decision to proceed to valve surgery is based on evidence of decompensation, either in the form of developing symptoms or by detecting a decrease in LV function or severe LV dilatation on echocardiography. There are a number of difficulties with approach in clinical practice. Like many valve lesions, chronic aortic regurgitation is normally very well tolerated for many years and hence the exact onset of symptoms can be extremely difficult to define. In addition echocardiographic assessment of AR severity can be challenging and there is often significant inter-observer variation in the calculation of LV volumes. Similarly as above, waiting for an otherwise asymptomatic patient to develop significant LV dilatation and or early LV dysfunction may put the patient at risk of increased perioperative complications and a worse long term outcome.

6.5.1 BNP AND AR SEVERITY

The measurement of BNP in otherwise asymptomatic patients may therefore be useful when symptoms or signs are equivocal. However relatively few prior studies have systematically assessed the factors which influence BNP release in patients with

AR. Weber et al evaluated the relationship between NT-BNP concentrations and the progression of disease in 37 patients with chronic aortic regurgitation and an EF >45% undergoing clinical follow up [Weber *et al* 2005]. They demonstrated a strong correlation between AR severity and NT-BNP concentrations, and a significant reduction in NT-BNP concentrations after valve surgery. Similarly, Eimer et al demonstrated an association between plasma concentrations of BNP and the severity of AR [Eimer *et al* 2004]. However these studies predominantly included patients with mild to moderate AR. This study found an association between plasma BNP concentrations and several echocardiographic measures of AR severity in a cohort of patients with moderate-to-severe or severe AR. Consequently an elevated BNP in the absence of an alternative cause in patients with AR should prompt further investigation of AR severity if echocardiographic parameters are difficult to assess or are indeterminate.

6.5.2 BNP AND LV REMODELING

Gerber et al [Gerber *et al* 2003] evaluated 40 patients with chronic AR from outpatient clinics and those meeting criteria for valve surgery. In this population of patients with markedly dilated ventricles, there was no correlation between BNP concentrations and LV dimensions and volumes at rest. Similarly, we demonstrated that compensatory LV remodeling may occur in asymptomatic AR patients with normal BNP concentrations. Indeed many AR patients had markedly increased and LV end-systolic and diastolic volumes and LV mass compared with normal controls. Despite this, many of these patients were relatively asymptomatic and had plasma

BNP concentrations that remained within the normal range. This limits the ability of BNP to detect patients prior to the development of LV remodeling.

6.5.3 BNP AND EXERCISE CAPACITY

Although the study by Gerber et al demonstrated higher BNP concentrations in symptomatic patients with AR, no study has assessed the relationship between concentrations of BNP and exercise treadmill capacity. Previous studies suggest that reporting of symptoms does not necessarily correlate with exercise capacity [Das *et al* 2005]. Exercise capacity can be influenced by factors other than cardiac function, and there can be considerable individual variation in physical fitness. For this reason a direct measure of early LV dysfunction may be preferred.

Prognostic studies have demonstrated worse outcome in AR patients with an impaired haemodynamic response to exercise [Borer *et al* 1998, Wahi *et al* 2000]. In the current study, patients with elevated BNP concentrations had several echocardiographic measures suggesting LV dysfunction immediately after exercise. AR patients with elevated BNP had higher LV end-systolic and end-diastolic volume index and a trend to lower post-exercise ejection fraction than AR patients with normal BNP concentrations. However, the predictive value of BNP and for post-exercise LV dysfunction on echocardiography was modest. Further research will be needed to determine whether BNP has prognostic value better than or additional to exercise stress echocardiography.

Strain rate is a less load-dependent marker of myocardial contractility [Marwick 2006] which has been associated with subclinical myocardial dysfunction and poorer post-operative outcome in patients with organic mitral regurgitation [Lee *et al* 2004]. In the current study, patients with elevated BNP concentrations had lower global longitudinal strain rate and change in strain rate after exercise. These observations suggest that measurement of BNP may identify early LV dysfunction in patients with severe AR, which may not be evident on resting echocardiography alone.

6.5.4 BNP AND TISSUE DOPPLER S' VELOCITIES

Two previous studies have investigated the role of long axis contraction (S') in asymptomatic patients with AR [Paraskevaidis *et al* 2006, Vinereanu *et al* 2001]. The presence of an S' velocity of the mitral annulus <9 cm/s has been associated with poorer exercise tolerance and a higher LV end-diastolic pressure and end-diastolic wall stress on cardiac catheterisation. However, there was no significant association between S' velocity at rest or post-exercise and the plasma concentration of BNP in this study.

6.5.5 STUDY LIMITATIONS

The number of patients studied was modest. However, it is unlikely that the association between BNP and post-exercise LV dysfunction was due to chance alone because there were associations between several post-exercise measures of LV dysfunction and BNP. On average patients were younger than in some previous

reports. This may reflect the larger proportion of patients with rheumatic heart disease who develop AR at an earlier age. Plasma concentrations of natriuretic peptides increase with age [Galasko *et al* 2005, Redfield *et al* 2002] but after adjustment for age, the associations between BNP and post-exercise LV function were stronger, and other associations were similar. The study was too small to allow meaningful subgroup analyses, for example of patients with no and mild symptoms. For asymptomatic patients with normal LV function, the rate of progression to symptoms or overt LV dysfunction is on average about 6% per year [Bonow *et al* 2006]. A much larger study with long-term follow-up is therefore needed to determine whether BNP can reliably predict outcomes.

6.6 CONCLUSION

This study suggests that AR patients with elevated BNP concentrations are more likely to have early LV dysfunction after exercise, but the clinical significance of these changes is currently uncertain. A large prospective study is needed to determine whether including serial measurements of BNP or NT-BNP during follow up improves the ability to detect early LV dysfunction and thereby allows more optimal timing of aortic valve replacement.

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CHAPTER SEVEN

NATRIURETIC PEPTIDES IN DIFFERENT VALVE LESIONS

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Plasma brain natriuretic peptide concentrations in
patients with valvular heart disease
(Open Heart- In Press)

7.1 SUMMARY

Plasma brain natriuretic peptide (BNP) concentrations predict prognosis in patients with valvular heart disease (VHD) but it is unclear whether this directly relates to disease severity. We assessed the relationship between BNP and echocardiographic measures of disease severity in patients with VHD. Plasma BNP concentrations were measured in patients with normal left ventricular (LV) systolic function and isolated VHD (mitral regurgitation, MR, n=33; aortic regurgitation, AR, n=39; aortic stenosis, AS, n=34; mitral stenosis, MS, n=30), and age- and sex-matched controls (n=39) immediately prior to exercise stress echocardiography.

Compared to controls, patients with VHD had elevated plasma BNP concentrations [(MR median 35 (IQR 23-52), AR 34 (22-45), AS 31 (22-60), MS 58 (34-90); controls 24 (16-33) pg/mL; $p<0.01$ for all]. LV end diastolic volume index varied by valve lesion; [MR (mean 77±14), AR (91±28), AS (50±17), MS (43±11), controls (52±13) mL/m^2; $p<0.0001$]. There were no associations between LV volume and BNP. Left atrial (LA) area index varied [MR (18±4 cm^2/m^2), AR (12±2), AS (11±3), MS (19±6), controls (11±2); $p<0.0001$], but correlated with plasma BNP concentrations: MR ($r=0.42$, $p=0.02$), MS ($r=0.86$, $p<0.0001$), AR ($r=0.53$, $p=0.001$) and AS ($r=0.52$, $p=0.002$). Higher plasma BNP concentrations were associated with increased pulmonary artery pressure and reduced exercise capacity. Despite adverse cardiac remodelling, 81 (60%) patients had a BNP concentration within the normal range.

Despite significant LV remodelling, plasma BNP concentrations are often normal in patients with VHD. Conversely, mild elevations of BNP occur with LA dilatation in the presence of normal LV. Plasma BNP concentrations should be interpreted with caution when assessing patients with VHD.

7.2 INTRODUCTION

Plasma BNP is a powerful prognostic marker in patients with a broad range of cardiac diseases including acute [Metra *et al* 2007] and chronic heart failure [McDonagh *et al* 2001, Rodeheffer 2004] and post myocardial infarction [Richards *et al* 1998]. Plasma concentrations of BNP may also increase in patients with valvular heart disease [Arat-Ozkan *et al* 2005, Detaint *et al* 2005, Gabriel *et al* 2008, Gerber *et al* 2003, Gerber *et al* 2003, Sharma *et al* 2011, Sutton *et al* 2003, Weber *et al* 2004], particularly in patients with symptoms and more severe valve lesions. Higher concentrations of BNP are associated with a worse outcome in patients with mitral regurgitation [Pizarro *et al* 2009] and aortic stenosis [Lancellotti *et al* 2010]. Patients with valve disease who have significant LV impairment often have very high concentrations of BNP [Detaint *et al* 2006, Nessmith *et al* 2005] but in these patients the indications for surgery are already clear. Measurement of BNP may however be useful in patients with heart valve disease and preserved left ventricular (LV) systolic function, especially when symptoms and haemodynamic data are equivocal.

7.2.1 PREVIOUS STUDIES ASSESSING NATRIURETIC PEPTIDES IN VHD

Previous studies have evaluated the relationship between plasma BNP concentrations and echocardiographic measures of disease severity as well as clinical outcomes for specific valve lesions including aortic stenosis, aortic regurgitation, mitral regurgitation and mitral stenosis [Gabriel *et al* 2008, Kerr *et al* 2008, Sharma *et al* 2011, Van Pelt *et al* 2008]. However, each aortic and mitral valve lesion causes

different cardiac pressure and volume loads, and it is unclear whether the mechanism of BNP release and clinical implications of elevated plasma BNP concentrations are dependent on valve lesion type. These previous studies did not directly compare patients with different valve lesions, which result in different volume and pressure loads on the heart.

7.2.2 STUDY AIMS

The aim of this study was to identify both common and valve lesion specific factors associated with higher plasma BNP concentrations in patients with preserved LV systolic function, who have isolated aortic stenosis (AS), aortic regurgitation (AR), mitral regurgitation (MR) or mitral stenosis (MS) and to assess suitability of BNP for identifying patients with severe VHD across different valve lesions.

7.3 METHODS

7.3.1 STUDY POPULATION

Patients with moderate to severe AS (peak velocity >3.0 m/s), moderate-to-severe AR (left ventricular outflow tract (LVOT) width ratio >0.3 and holodiastolic flow reversal in descending thoracic aorta), moderate-to-severe MS (mitral valve area <1.5 cm^2), and moderate-severe or severe MR (effective regurgitant orifice area >0.3 cm^2) were identified from echocardiogram reports and out-patient clinics in the Auckland region [Baumgartner *et al* 2009, Zoghbi *et al* 2003]. All patients had normal left ventricular ejection fraction (AS ≥ 50%, AR >50%, MR ≥ 60%, MS≥ 50)

[Bonow *et al* 2006]. Exclusion criteria included ischaemic heart disease, significant renal impairment (creatinine >160 µmol/L on baseline blood tests performed at enrolment), respiratory disease, and an inability to walk on a treadmill or a contraindication to exercise testing. All patients eligible for inclusion were invited to participate. The patients' symptomatic status was assessed according to the New York Heart Association criteria by a cardiologist blinded to echocardiographic data and peptide levels at the time of enrolment. Control subjects were volunteers from the local community who were age and sex matched. They were recruited by advertisement and had no clinical evidence of cardiovascular or respiratory disease.

7.3.2 EXERCISE TESTING

All patients underwent symptom-limited exercise testing on a motorized treadmill. A standard Bruce protocol was used for patients with mitral regurgitation. However it was noted that there was significant clustering of exercise times at the end of each stage and this was felt to affect adversely the objectivity of the determination of exercise capacity. Consequently for subsequent patients, the protocol was adjusted so that the speed and/or incline of the treadmill were increased at 1-min intervals. The maximum workload at the end of each 3-min stage remained equivalent to that of the standard Bruce protocol. Exercise was stopped for significant dyspnoea, chest discomfort, pre-syncope, fatigue or at patient request.

7.3.3 ECHOCARDIOGRAPHY

All echocardiograms were performed by experienced sonographers on modern cardiac ultrasound machines (Vivid 7, General Electric, Vingmed Ultrasound,

Norway). All patients underwent comprehensive examination including M-mode, 2-dimensional, Doppler and tissue Doppler echocardiography modified according to their underlying valvular lesions consistent with current guidelines [Baumgartner *et al* 2009, Zoghbi *et al* 2003]. All analysis was performed offline (Echopac PC version 4.0.0 GE Medical, Milwaukee, WI) by an experienced cardiologist blinded to the results of the patient characteristics and BNP data. All measurements were averaged from at least 3, or in cases of atrial fibrillation (AF), 5 cardiac cycles. The left ventricular (LV) end-systolic and end-diastolic volumes and ejection fraction (EF) were measured from the apical four-chamber view using the modified Simpson's single-plane method [Leung *et al* 1996]. This method was chosen to allow comparison with the post-exercise volumes. The left atrial area was measured in the apical four-chamber view [Lester *et al* 1999].

Assessment Of Valve Severity

Quantitative and qualitative measures of aortic stenosis and regurgitation severity were made according to ASE guidelines [Baumgartner *et al* 2009, Zoghbi *et al* 2003]. Quantitative measures of AS severity included peak velocity, mean pressure drop and aortic valve area. Assessment of AR severity included the AR jet:LVOT width ratio, AR pressure half time, peak diastolic and end-diastolic flow velocities in the descending thoracic and abdominal aorta.

The severity of MR was assessed by quantitative Doppler with mitral and aortic stroke volumes [Enriquez-Sarano *et al* 1993] and by the PISA method [Enriquez-Sarano *et al* 1995]. The stroke volumes obtained from the two methods were averaged to give a mean regurgitant volume [Detaint *et al* 2005]. The mitral valve

area (MVA) was obtained using direct planimetry, pressure half time, and continuity methods [Hatle *et al* 1978, Martin *et al* 1979, Nakatani *et al* 1988]. The median MVA from these three methods was used for analysis. Mean trans-mitral pressure gradients were obtained by tracing the continuous wave Doppler signal across the mitral valve [Quinones *et al* 2002].

Estimation Of Pulmonary Artery Pressure

Agitated saline was used to facilitate the estimation of pulmonary artery pressure as described in Chapter 2.

7.3.4 MEASUREMENT OF NATRIURETIC PEPTIDES.

Blood samples were obtained from an indwelling intravenous catheter after 15 min lying supine, immediately prior to the baseline echocardiogram and immediately post exercise. Patients fasted for 2 hours prior to the investigations. Blood samples were collected in EDTA tubes and plasma stored at –80 °C and for measurement BNP concentrations at the study end using established radioimmunoassays [Yandle *et al* 1993]. The upper limit of the normal reference range for BNP is 42 pg/mL. To convert BNP levels expressed in pg/mL to pmol/L, divide by 3.47 [Van Pelt *et al* 2007, Yandle *et al* 1993].

7.3.5 STATISTICAL ANALYSIS.

Previous studies have demonstrated a mean plasma BNP concentration of 22±7 pg/mL in the normal healthy population [Yandle *et al* 1993]. A minimum sample

size of 30 in each valve subgroup was required to detect a 20% increase in plasma BNP concentrations compared to controls (power of 80% and alpha=0.01). Categorical data were presented as frequency and percentage, and continuous data were presented as mean ± standard deviation (SD), or median and inter-quartile range (IQR). BNP underwent natural log transformation in analyses due to its right skewed distributions unless specified, and was reported as median and inter-quartile range. Comparison of all valves versus the control group, and valve sub-groups was performed using the Chi-square or Fisher's exact tests for categorical data where appropriate. For continuous variables, two independent sample Student's t-test or non-parametric Mann-Whitney *U* test was used, where appropriate for comparing all valves versus controls group. For comparison between subgroup of valves, one-way analysis of variance (ANOVA) was performed followed by the Dunnett's test, to compare each valve subgroup with control subjects. The Kruskal-Wallis test was used when the continuous data was not normally distributed. Pearson correlation coefficients were reported for linear associations. All p-values reported were two tailed and a p-value <0.05 was considered significant. Data was analysed using SAS statistical package, version 9.1.3 (SAS Institute, Cary, NC).

7.4 RESULTS

7.4.1 BASELINE CHARACTERISTICS

All patients who agreed to participate completed all aspects of the study. One hundred and seventy five subjects with isolated MR (n=33), AR (n=39), AS (n=34) and MS (n=30) or normal valves (n=39) were studied. Plasma BNP concentrations and exercise treadmill data was available for all patients. Plasma BNP concentrations (median, inter-quartile range) were elevated in all valve lesions compared to controls [MR (35 pg/mL, 23-52), AR (34 pg/mL, 22-45), AS (31 pg/mL, 22-60), MS (58 pg/mL, 34-90), Controls (24 pg/mL, 16-33); $p<0.01$ for all]. For each valvular lesion, patients were divided into two groups depending on whether the plasma BNP concentration was within the normal range or elevated (>42 pg/mL).

Patients with AS were predominantly male whereas patients with MS were predominantly female (Table 7.1). In keeping with the higher proportion of degenerative valve disease, AS patients were generally older than those with other valve lesions. Patients with mitral valve disease had a higher plasma BNP concentration than those with aortic valve disease (46 (29-73) vs. 32 (22-49) pg/mL, $p=0.012$). For each given valve lesion, patients with MS had the highest plasma concentration of BNP. This remained the case if patients with AF were excluded from the analysis (BNP in MS with sinus rhythm 55 (30-73) vs. other valve lesions 34 (22-52) pg/ml; $p=0.02$.

The relative use of cardiac medication differed between valve groups. Patients with aortic regurgitation were the most likely to be taking medication with 64% of patients

taking an angiotensin converting enzyme inhibitor. Forty-three percent of MS patients were taking a loop diuretic (at a dose of 40mg furosemide or less) and 32% of patients with AS were taking a betablocker. Patients with AS who were not taking a betablocker had lower plasma BNP concentrations than those that were [26(20,41) vs. 42 (34,63); p=0.03]. There was no other statistically significant difference in plasma BNP concentrations between patients that were taking medication compared to those that were not in any other valve subgroup

Table 7.1. Baseline characteristics, baseline echocardiographic and exercise data

[1] P-value relates to All Valves patients compared to controls, [2] P-value for comparison between subgroups.
* Comparison significant at the 0.05 level between each valve group versus controls

	Controls	MR	MS	AS	AR	All Valves	P-value[1]	P-value[2]
Number of subjects	39	33	30	34	39	136	-	-
Age, (years)	55 ± 15	53 ± 16	49 ± 14	67 ± 9*	42 ± 14*	53 ± 16	0.404	<0.001
Female, n (%)	16 (41)	15 (45)	28 (93)	4 (12)	6 (15)	53 (39)	0.817	<0.001
Body mass index (kg/m^2)	25.8 ± 3.5	27.7 ± 5.0	28.6 ± 5.8	28.9 ± 4.5*	28.8 ± 4.7*	28.5 ± 4.9	0.001	0.023
Atrial fibrillation, n (%)	0 (0)	0 (0)	8 (27)	0 (0)	0 (0)	8 (6)	0.202	<0.001
Symptomatic, n (%)	1 (3)	17 (52)	14 (47)	17 (50)	7 (18)	55 (40)	<0.001	<0.001
Medication, n (%)								
Loop diuretic	0 (0)	4 (12)	13 (43)	5 (15)	2 (5)	24 (18)	0.003	<0.001
ACE Inhibitor	0 (0)	6 (18)	4 (13)	4 (12)	25 (64)	39 (29)	<0.001	<0.001
Beta Blocker	0 (0)	6 (18)	4 (13)	11 (32)	2 (5)	23 (17)	0.006	<0.001
BNP (pg/mL)	24 (16-33)	35 (23-52)	58 (34-90)	31 (22-60)	34 (22-45)	36 (24-62)	<0.001	<0.001
Left atrial area index	10.5 ± 1.9	17.5 ± 4.4*	19.3 ± 5.9*	11.5 ± 2.5	10.8 ± 2.0	14.5 ± 5.4	<0.001	<0.001
LVEDVI (ml/m^2)	52.3 ± 12.7	76.6 ± 14.0*	43.4 ± 11.2	49.6 ± 16.5	91.3 ± 28.4*	66.9 ± 27.6	0.003	<0.001
LVESVI (ml/m^2)	19.0 ± 7.1	26.9 ± 6.5*	16.5 ± 5.9	20.8 ± 12.3	33.9 ± 14.1*	25.1 ± 12.4	0.005	<0.001
LVEF (%)	64.5 ± 7.6	64.6 ± 6.7	62.4 ± 7.3	61.9 ± 7.0	63.7 ± 6.3	63.2 ± 6.8	0.320	0.380
PA Pressure (mmHg)	24 ± 4	37 ± 13*	36 ± 12*	32 ± 7*	28 ± 7	33 ± 10	<0.001	<0.001
Peak heart rate (bpm)	153 ± 16	153 ± 21	148 ± 24	129 ± 20*	133 ±19*	140 ± 23	0.0003	<0.001
Exercise capacity (METS)	12.5 ± 3.1	9.1 ± 2.7*	6.3 ± 2.6*	9.1 ± 3.2	10.9 ± 3.4*	9.0 ± 3.4	<0.001	<0.001
Peak systolic BP (mmHg)	169 ± 23	163 ± 30	132 ±23*	159 ± 22	188 ±24*	163 ± 32	0.183	<0.001

LVEDVI:Left ventricular end-diastolic volume index, LVESVI: left ventricular end-systolic volume index, LVEF: Left ventricular ejection fraction ,PA pulmonary Artery, BP: blood pressure, BNP :Brain Natriuretic Peptide. Results are Mean±SD except BNP which is median (IQR)

7.4.2 ADVERSE CARDIAC REMODELING.

Although all subjects had a normal LV ejection fraction, LV end diastolic volume index (LVEDVI) varied considerably across patients and by valve lesion: MR 77±14, AR 91±28, AS 50±17, MS 43±11, and controls 52±13 mL/m^2; p<0.0001). For each valvular lesion, patients were divided into two groups depending on whether the plasma BNP concentration was within the normal range (≤42 pg/mL) or elevated. The relative numbers of patients with elevated BNP in each group are shown in Table 7.2. Even when plasma BNP concentration remained within the normal range (<42 pg/mL), those with regurgitant valve lesions had significant LV dilatation compared to controls: (LVEDVI in MR 78±14, AR 88±27 and controls 52±12 mL/m^2; p= <0.0001). There was no association between any resting measure of LV function and plasma BNP concentration (Table 7.3).

LA area index (LAAI) was greater in patients with mitral compared to aortic valve disease: [MR 17±4, MS 19±6, AR 11±2, AS 11±2,) and controls (11±2 cm^2/m^2, p<0.0001). Despite no association with markers of LV size, there, there was a consistent correlation with LAAI across all valve lesions: MR (r=0.42, p=0.02), MS (r=0.86, p<0.0001), AR (r=0.53, p=0.001), AS (r=0.52, p=0.002), all valves (r=0.57, p<0.0001). An increase in plasma BNP concentration was also associated with a higher pulmonary artery pressure in all valve lesions (Tables 7.2 and 7.3).

Table 7.2. Measures of cardiac remodelling, valve severity and exercise capacity for each valve lesion stratified by BNP

		Controls	Aortic Stenosis	Mitral Stenosis	Aortic Regurgitation	Mitral Regurgitation
Number Of Subjects	Normal BNP	34	24	10	29	21
	High BNP	5	10	20	10	12
	Total	39	34	30	29	33
NYHA Class 2, n (%)	Normal BNP	1 (2.9)	8 (33.3)	3 (33.3)	3 (10.3)	7 (33.3)
	High BNP	0 (0)	7 (70.0)	11 (55.0)	2 (20.0)	8 (66.7)
	P-value	1.00	0.20	0.26	**0.03**	0.09
Severe Valve Disease n (%)	Normal BNP	-	3 (13)	1 (10)	15 (52)	15 (71)
	High BNP	-	5 (50)	4 (20)	9 (90)	6 (50)
	P-value	-	**0.03**	0.64	0.06	0.27
LV End-Diastolic Volume Index (ml/m^2)	Normal BNP	52 ± 12	50 ± 17	45 ± 7	88 ± 27	78 ± 14
	High BNP	53 ± 16	48 ± 17	42 ± 13	100 ± 31	75 ± 14
	P-value	0.96	0.73	0.50	0.20	0.59
LV End-Systolic Volume Index (ml/m^2)	Normal BNP	19 ± 7	19 ± 9	16 ± 5	32 ± 13	28 ± 6
	High BNP	19 ± 6	24 ± 19	16 ± 6	39 ± 17	26 ± 7
	P-value	0.89	0.95	0.91	0.25	0.81
LV Ejection Fraction (%)	Normal BNP	64 ± 8	61 ± 7	63 ± 8	64 ± 6	64 ± 7
	High BNP	65 ± 9	63 ± 6	62 ± 7	63 ± 6	66 ± 7
	P-value	0.90	0.47	0.57	0.54	0.57
LA Area Index (cm^2/m^2)	Normal BNP	10 ± 2	11 ± 2	15 ± 2	10 ± 2	17 ± 4
	High BNP	11 ± 3	13 ± 3	21 ± 6	12 ± 2	18 ± 5
	P-value	0.69	**0.008**	**0.0005**	0.07	0.47
Pulmonary Artery Pressure (mmHg)	Normal BNP	24 ± 4	31 ± 6	34 ± 16	27 ± 6	32 ± 7
	High BNP	25 ± 6	35 ± 7	36 ± 9	32 ± 6	47 ± 16
	P-value	0.77	0.16	0.14	0.06	**0.008**
Valve Area Index/EROA Index (cm^2/m^2)	Normal BNP	-	0.51 ± 0.13	0.75 ± 0.15	0.10 ± 0.07	0.34 ± 0.16
	High BNP	-	0.41 ± 0.09	0.62 ± 0.14	0.16 ± 0.08	0.32 ± 0.16
	P-value		**0.04**	**0.03**	**0.02**	0.72
Exercise Capacity (METs),	Normal BNP	12 ± 3	10 ± 3	8 ± 3	11 ± 4	10 ± 2
	High BNP	14 ± 3	7 ± 2	5 ± 2	11 ± 3	7 ± 2
	P-value	0.22	**0.003**	**0.02**	0.65	**0.001**

NYHA: New York Heart Association; LV: left ventricle; LA: left atrium; EROA: effective regurgitant orifice area. BNP: brain natriuretic peptide.
All data is mean ± SD unless otherwise stated. P values relate to comparison of Normal vs raised BNP groups

Table 7.3. Associations between brain natriuretic peptide concentrations, echocardiographic variables and exercise capacity.

	Controls r, (p)	**Aortic Stenosis r, (p)**	**Mitral Stenosis r, (p)**	**Aortic Regurgitation r, (p)**	**Mitral Regurgitation r, (p)**	**All valves r, (p)**
LV End-Diastolic Volume Index (mL/m^2)	0.22, (0.20))	0.02, (0.93)	-0.24, (0.20)	0.16, (0.34)	-0.02, (0.28)	-0.01, (0.85)
LV End-Systolic Volume Index (mL/m^2)	0.13, (0.43)	0.10, (0.59)	-0.06, (0.74)	0.19, (0.24)	-0.19, (0.31)	0.01, (0.86)
Left Atrial Area Index (cm^2/m^2)	0.10, (0.57)	**0.52, (0.002)**	**0.86 (<0.0001)**	**0.53, (0.001)**	**0.42 (0.02)**	**0.57, (<0.0001)**
Pulmonary Artery Pressure (mmHg)	0.29, (0.08)	**0.40 (0.037)**	**0.47 (0.008)**	**0.39, (0.02)**	**0.53 (0.002)**	**0.36, (<0.0001)**
Valve Area/EROA Index (cm^2/m^2)	-	-0.28 (0.10)	-0.23 (0.21)	0.22 (0.18)	-0.05, (0.79)	-
Exercise Capacity [METS]	0.23, (0.16)	**-0.44, (0.009)**	**-0.56 (0.001)**	-0.11, (0.52)	**-0.53 (0.001)**	**-0.38, (<0.0001)**

LV: Left ventricle; EROA: Effective Regurgitant Orifice Area; BNP: Brain Natriuretic Peptide. Pearson's correlation used for analysis

7.4.3 EXERCISE CAPACITY AND FUNCTIONAL STATUS

Across all valve lesions, 55 (40%) patients were symptomatic and were more likely to have a raised plasma BNP concentration than those who remained asymptomatic (49 (32-79) vs. 31 (22-44) pg/mL; p<0.001). Patients who were symptomatic had higher pulmonary artery pressures (38±12 vs. 29±8 mmHg; p<0.001), larger left atrial area index (16±6 vs. 14±5 cm^2/m^2; p=0.02), and lower exercise capacity (7.1±2.4 vs. 10.4±3.4 METS; p<0.001) than asymptomatic subjects. However this finding was not consistent across all valve subgroups and in particular although asymptomatic patients with MS and AR had slightly higher exercise capacity than those with mild symptoms, this was not statistically significant (Table 7.4). Patients with an elevated BNP performed less well on the treadmill than those with a normal BNP (10.1±3.1 vs. 7.2±3.1 METS, p<0.0001). This finding was consistent and statistically significant for all valve subgroups except for those with AR (table 2).

However the patients with poor exercise capacity identified by NYHA class and those by an elevated plasma BNP concentration were not identical. Of the 81 patients in NYHA class 1, twenty patients had an elevated BNP. These patients performed less well on the treadmill than asymptomatic patients in whom BNP remained within the normal range (10.9±3.1 vs. 8.7±3.8 METS, p=0.01)

Table 7.4. Characteristics of asymptomatic vs. symptomatic patients (mean ± SD unless otherwise stated)

		Controls	Aortic Stenosis	Mitral Stenosis	Aortic Regurgitation	Mitral Regurgitation
Number Of Subjects	NYHA 1	39	17	16	32	16
	NYHA 2		17	14	7	17
	Total	39	34	30	39	33
BNP pg/mL	NYHA 1	26.8 ± 13.0	33.7 ± 19.3	60.2 ± 45.9	40.9 ± 37.7	33.6 ± 19.4
	NYHA 2	-	45.0 ± 24.8	86.1 ± 50.4	74.2 ± 75.9	52.3 ± 29.7
	P value		0.19	0.08	0.10	**0.04**
Severe Valve Disease n (%)	NYHA 1	-	2 (12)	1 (6)	19 (58)	13 (81)
	NYHA 2	-	6 (35)	4 (29)	5 (71)	8 (47)
	P value		0.22	0.16	0.69	**0.04**
LV End-Diastolic Volume Index (ml/m^2),	NYHA 1	52.3 ± 12.7	52.8 ± 14.4	46.9 ± 9.6	90.3 ± 28.6	80.5 ± 11.2
	NYHA 2	-	46.6 ± 18.1	39.4 ± 11.8	95.7 ± 29.5	72.9 ± 15.6
	P value		0.28	0.07	0.57	0.12
LV End-Systolic Volume Index (ml/m^2)	NYHA 1	19.0 ± 7.1	18.7 ± 7.6	17.9 ± 6.1	33.3 ± 13.7	28.3 ± 6.4
	NYHA 2	-	22.8 ± 15.4	14.9 ± 5.4	36.7 ± 16.8	25.6 ± 6.5
	P value		0.61	0.18	0.50	0.61
LV Ejection Fraction (%)	NYHA 1	65 ± 8	63 ± 8	62 ± 9	64 ± 6.2	65 ± 7
	NYHA 2	-	61 ± 6	63 ± 4	63 ± 7	65 ± 6
	P value		0.32	0.86	0.80	0.96
LA Area Index (cm^2/m^2)	NYHA 1	10.6 ± 1.9	11.5 ± 2.5	18.2 ± 6.0	10.6 ± 2.0	17.4 ± 3.9
	NYHA 2	-	11.4 ± 2.6	20.5 ± 5.9	11.8 ± 2.0	17.6 ± 5.0
	P value		0.90	0.16	0.14	0.73
Pulmonary Artery Pressure (mmHg)	NYHA 1	25 ± 4	30 ± 7	32 ± 14	28 ± 6	32 ± 6
	NYHA 2	-	35 ± 6	40 ± 8	31 ± 9	42 ± 16
	P value		0.06	**0.01**	0.19	**0.03**
Valve Area Index/EROA Index (cm^2/m^2)	NYHA 1	-	0.51 ± 0.09	0.71 ± 0.15	0.11 ± 0.07	0.38 ± 0.16
	NYHA 2	-	0.45 ± 0.14	0.62 ± 0.16	0.16 ± 0.07	0.29 ± 0.15
	P value		0.15	0.13	0.06	0.10
Exercise Capacity (METS)	NYHA 1	12.6 ± 3.1	10.9 ± 2.8	7.0 ± 3.0	11.3 ± 3.6	11.1 ± 1.6
	NYHA 2	-	7.4 ± 2.5	5.5 ± 2.0	9.4 ± 1.9	7.2 ± 2.1
	P value		**0.003**	0.19	0.26	**<0.0001**

NYHA: New York Heart Association; LV: left ventricle; LA: left atrium; EROA: effective regurgitant orifice area. BNP: brain natriuretic peptide.
All data is mean ± SD unless otherwise stated. P values relate to comparison of NYHA 1 vs. NYHA 2 groups.

7.4.4 PLASMA BNP CONCENTRATIONS POST EXERCISE

Plasma BNP concentrations taken immediately post exercise were higher across the whole cohort of patients with VHD (43 (28,75) vs. 33 (22,55) pg/mL, p=0.003). However in the individual valve lesions groups, only patients with MR had a higher concentration of BNP (Table 7.5). In addition a small rise in plasma BNP concentrations was seen in the control group.

There was a strong association between plasma BNP concentrations taken at rest and post exercise (r=0.92, p=<0.0001). Across all valves the correlation with plasma BNP and left atrial area index, pulmonary artery pressure and exercise capacity observed at rest were also seen with plasma BNP taken post exercise (Table 7.6). The measurement of plasma BNP concentrations post exercise did not offer any additional information over plasma BNP concentrations measured at rest.

Table 7.5. Plasma concentrations of BNP at rest and immediately post exercise

	BNP Baseline Median (IQR) (pg/mL)	**BNP post exercise Median (IQR) (pg/mL)**	**p value**
Controls (n=39)	**24 (16,33)**	**33 (21, 43)**	**0.03**
Mitral Regurgitation (n=33)	**35 (23,52)**	**54 (35, 94)**	**0.03**
Mitral Stenosis (n=30)	58 (34,90)	71 (43,108)	0.36
Aortic Stenosis (n=34)	31 (22,60)	40 (26,75)	0.10
Aortic Regurgitation (n=39)	34 (22,45)	43 (27,63)	0.16
All Valves (n=136)	**36 (24,62)**	**43 (28,75)**	**0.003**

Table 7.6. Associations between BNP post exercise, echocardiographic variables and exercise capacity.

	Controls r, (p)	**Aortic Stenosis r, (p)**	**Mitral Stenosis r, (p)**	**Aortic Regurgitation r, (p)**	**Mitral Regurgitation r, (p)**	**All valves r, (p)**
LV end-diastolic volume index (mL/m^2)	0.24, (0.15)	0.07, (0.72)	-0.34, (0.07)	0.17, (0.29)	0.04, (0.81)	-0.06, (0.48)
LV end-systolic volume index (mL/m^2)	0.10, (0.58)	0.18, (0.30)	-0.16, (0.42)	0.20, (0.29)	-0.08, (0.67)	-0.01, (0.92)
Left atrial area index (cm^2/m^2)	0.31, (0.07)	0.47, (0.006)	**0.66, (<0.0001)**	**0.52, (0.001)**	**0.43, (0.01**)	**0.52, <0.0001)**
Pulmonary Artery Pressure (mmHg)	0.32, (0.05)	0.33, (0.09)	0.23, (0.24)	**0.40, (0.01)**	**0.42, (0.02)**	**0.36, (<0.0001)**
Valve area/EROA index (cm^2/m^2)	-	-0.22, (0.21)	-0.33, (0.08)	0.20, (0.22)	0.13, (0.51)	-
Exercise Capacity [METS]	0.18, (0.29)	-0.29, (0.10)	-0.44, (0.02)	-0.10, (0.54)	-0.32, (0.07)	**-0.33, (<0.0001**)

LV: Left ventricle; EROA: Effective Regurgitant Orifice Area; BNP: Brain Natriuretic Peptide. Pearson's correlation used for analysis

7.5 DISCUSSSION

This study evaluated associations between the plasma BNP concentrations and echocardiographic measures of LV and LA remodelling in patients with moderate to severe aortic and mitral valve disease. Patients with impaired LVEF were excluded so that the impact of factors other than LV systolic function could be evaluated. There were several clinically relevant observations. First, whilst there was a wide range of LV remodelling across different valve lesions, there was no correlation between the plasma BNP concentration and LV end systolic or end diastolic volumes for any valve lesion. This implies that in VHD patients with normal ejection fraction, compensatory LV remodelling is not associated with an increase in plasma BNP concentration. Second, the plasma BNP concentration correlated with LA size in all valve lesions. Third, plasma BNP concentrations were higher in subjects with mitral compared to aortic valve disease, and highest in patients with mitral stenosis, in which setting there is no increase in LV wall stretch or pressure load. BNP also increased with higher pulmonary artery pressures. In these patients, the elevation in pulmonary artery pressure was likely to be secondary to an increase in LA filling pressure. These observations are consistent with BNP release from the LA in response to an increase in volume and wall stretch. This hypothesis is supported by evidence for synthesis of BNP by atrial myocytes in response to chronic increases in wall stress [Langenickel *et al* 2000] and co-storage of BNP with ANP in atrial granules [Goetze *et al* 2006].

In aortic valve disease, plasma BNP concentrations increased with relatively small increases in LA volume. It is possible that LA dilatation in aortic valve disease reflects subtle LV systolic or diastolic dysfunction. However assessment of diastolic function, particularly in patients with mitral valve disease is not well validated and comparison across valve lesions is not possible. In subjects with mitral valve disease, small increases in LA volume were often not associated with higher plasma BNP concentrations, but more marked LA enlargement usually was. Some patients with mitral stenosis were in atrial fibrillation, which is known to be associated with higher plasma BNP concentrations [Dussaule *et al* 1988, Engelmann *et al* 2005]. The number of patients with atrial fibrillation in this study was too small to allow a reliable analysis of the relationship between atrial fibrillation and BNP.

Higher plasma BNP concentration was associated with pulmonary hypertension in all valve subgroups. In addition higher BNP was associated with reduced exercise capacity for all valve lesions except for AR. Symptomatic patients with any valve lesion were more likely to have an elevated pulmonary artery pressure or a decreased exercise capacity. As this elevated pulmonary pressure and decreased exercise capacity are the objective correlates of symptomatic status, this is not surprising. However there was considerable overlap in the objective parameters between symptomatic and asymptomatic patients consistent with the known difficulties in assessing cardiac symptoms particularly in the early stages of decompensation [Messika-Zeitoun *et al* 2006]. Furthermore although both symptomatic patients and those with elevated plasma BNP concentrations tended to have objective evidence of exercise limitation or echocardiographic features of more advanced valve disease, the

patients identified were not identical. This suggests that plasma BNP concentrations may offer additional information in assessing the haemodynamic consequences of valve lesions in patients with AS, MS, and MR. We did not find similar associations between BNP and exercise capacity in patients with aortic regurgitation. The reason for the lack of a statistically significant association in the AR cohort is uncertain.

7.5.1 CLINICAL IMPLICATIONS

In this study, most patients with severe valve disease had a plasma BNP concentration of <100 pg/mL: a value below which cardiac failure is considered unlikely in patients presenting with dyspnoea [Dickstein 2008]. Patients with valve disease and a preserved LV ejection fraction may therefore have clinically important symptoms and pulmonary hypertension with a relatively modest increase in BNP. Conversely, in patients with other reasons for an elevated BNP, measuring plasma BNP concentration to assess valve status may not be helpful. In this study, patients with other known causes of an elevated BNP were excluded.

Previous studies which evaluate outcomes in patients with mitral regurgitation [Pizarro *et al* 2009] and aortic stenosis [Lancellotti *et al* 2010] suggest that an elevated BNP may identify patients who have a higher risk of adverse events. There is known difficulty in evaluating symptoms in some patients [Messika-Zeitoun *et al* 2006] and a significant number of asymptomatic patients in this study had an elevated plasma BNP concentration. These patients had a lower exercise capacity than those in whom the BNP remained within the normal range. Consequently

elevated plasma BNP concentrations in apparently asymptomatic patients should lead to a more careful assessment regardless of the type of valve lesion.

7.5.2 STUDY LIMITATIONS

The proportion of asymptomatic and symptomatic patients in each valve group differed but with the exception of the AR subgroup, at least half of the patients in each valve type had mild or equivocal symptoms. The small number of symptomatic patients in the AR subgroup may partly explain the lack of associations between BNP and exercise capacity in this group. In the AS subgroup only asymptomatic and patients with equivocal symptoms underwent exercise testing and in the other subgroups patients had at most mild symptoms as those with contraindications to exercise testing were excluded from the study. In particular patients with severe AS with symptoms of angina were excluded from the study. This selection of predominantly asymptomatic and mildly symptomatic patients may be responsible for the relatively modest rise in plasma BNP concentration in this cohort. However in clinical practice, patients with significant valve disease who have clear symptoms usually have a class 1 indication for surgery or valve intervention according to current guidelines [Bonow *et al* 2006, Vahanian *et al* 2007]. Consequently the measurement of BNP in these patients is unlikely to be helpful. A further limitation is that although the overall number of patients within this study is modest, the number of patients within each valve group is relatively small. This limits the power of further subgroup analysis or comparison against other markers of valve severity within each subgroup. Furthermore although valve severity was graded according to the ASE/EAE guidelines [Baumgartner *et al* 2009], the grading of severity,

particularly between regurgitant and stenotic lesions differs considerably and hence is not directly comparable.

7.6 CONCLUSION

In patients with isolated heart valve disease and a preserved ejection fraction, significant cardiac remodelling can occur whilst BNP remains within the normal range. However BNP increases with greater left atrial size and pulmonary artery pressure in all valve lesions. Consequently plasma BNP concentrations cannot reliably identify patients with significant valve disease and therefore should be interpreted with caution in these patients. However elevated BNP levels were associated with poor exercise capacity and therefore a raised BNP in an apparently asymptomatic patient with stable valve disease should prompt further assessment.

7.7 ACKNOWLEDGEMENTS

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CHAPTER EIGHT

CONCLUSIONS AND FUTURE DIRECTIONS

8.1 ASSESSMENT OF SYMPTOMS

This research demonstrates that the accurate assessment of symptomatic status in valvular heart disease can be extremely challenging. Regardless of the underlying type of valve lesion a significant number of patients who were deemed to be asymptomatic by an experienced cardiologist had significantly lower exercise capacity than aged matched controls on objective exercise testing. Of greater concern was the finding that a small but significant number had extremely poor exercise capacity and a number of adverse features on exercise stress echocardiography. This confirms our belief that we need additional methods to the current approach of assessing symptom status and resting echocardiographic parameters of severity.

8.2 EXERCISE ECHOCARDIOGRAPHY IN VHD

When performed in VHD patients without an indication for surgery based on symptomatic assessment and echocardiography performed at rest, exercise echocardiography identifies a high-risk cohort of patients who have an increased risk of death or hospitalisation of heart failure within 2 years. This is in keeping with other studies that have assessed the role of exercise electrocardiography in aortic stenosis [Alborino *et al* 2002, Amato *et al* 2001]. However although a few other studies have demonstrated that worsening of MR severity [Magne *et al* 2010] may be associated with an increased adverse events, there is little other published data linking the presence of adverse features on exercise stress echocardiography with reduced event free survival in other valve lesions. In this research the event rate was

too small to assess the role of exercise echocardiography in determining prognosis in individual valve lesions. However the findings suggest that exercise echocardiography can predict adverse outcome regardless of the underlying valve lesion and that there may be a role for routine exercise echocardiography in asymptomatic patients with valvular heart disease.

8.3 NATRIURETIC PEPTIDES IN VHD

8.3.1 NATRIURETIC PEPTIDES IN MITRAL STENOSIS

In contrast to other valve lesions, in MS the LV is not subject to increased wall stress. Consequently BNP, which was thought to be released predominantly from the left ventricle, was hypothesised to be unhelpful in the assessment of MS severity. ANP, which is predominantly released from the atria, appeared to have theoretical advantages in the assessment of MS. However we found that plasma BNP concentrations were significantly elevated in MS compared to controls and increased with MS severity. Indeed there was a fairly strong association with BNP and left atrial size and a weaker association with pulmonary artery pressure. In contrast there were no associations with any marker of left or right ventricular size or function. This suggests that atrial release of BNP may be an important factor in MS.

In addition BNP was found to be able to identify patients fulfilling the ACC/AHA [Bonow *et al* 2006] criteria for intervention with a cut off of twice the upper limit of normal have a reasonable sensitivity and specificity for identifying patients who may benefit from valve intervention. In addition a BNP level of greater than twice the

upper limit of normal was associated with a significantly increased risk of death, hospitalisation with heart failure or valve intervention.

A plasma ANP concentration of twice the upper limit of normal was also predictive of adverse outcome and again had reasonable sensitivity and specificity in identifying patients who fulfilled the ACC/AHA criteria for valve intervention. However plasma ANP concentrations performed marginally less well in this regard than BNP and did not provide significant additional information. Given that assays for BNP are more readily available there was little to favour using ANP in the assessment of MS.

8.3.2 NATRIURETIC PEPTIDES IN MITRAL REGURGITATION

In a cohort of MR patients with normal LV function who were either asymptomatic or had equivocal symptoms we found that a significant number of patients had plasma BNP levels that remained within the normal range. Despite this there was evidence of significant adverse cardiac remodelling with dilated left ventricles and enlarged atria. In addition the plasma BNP level was significantly associated with left atrial size and higher pulmonary artery pressures both at rest and immediately post exercise.

However plasma BNP concentrations were not associated with any marker of LV size or systolic function. This is in contrast to previous studies that have suggested that LV remodelling is the primary determinant of elevated plasma BNP concentrations in MR [Detaint *et al* 2006, Yusoff *et al* 2006]. In contrast to this

research, previous studies included patients with either LV dysfunction [Detaint *et al* 2006], significant symptoms or used a cut-off EF of >55% [Yusoff *et al* 2006] which in the context of severe MR represents mild LV dysfunction. In these patients the indication for valve surgery is already clear and the measurement of natriuretic peptides is unlikely to offer additional benefit.

One of the most striking findings in this study was the clear relationship between BNP and exercise capacity on treadmill testing. This is despite this being a relatively asymptomatic cohort of patients. Indeed in MR patients, plasma BNP concentrations above the normal range had a reasonable sensitivity and specificity for predicting pulmonary hypertension post exercise or impaired exercise capacity. Consequently although a normal plasma BNP cannot exclude severe MR with signs of adverse cardiac remodelling, even mild elevations of plasma BNP in an asymptomatic patient with MR should prompt further reassessment of the patient to ensure that the severity or the haemodynamic consequences are not being underestimated.

8.3.3 NATRIURETIC PEPTIDES IN AORTIC REGURGITATION

In a cohort of patients with moderate-severe or severe AR with normal LV function who were asymptomatic or had equivocal symptoms, plasma BNP concentrations often remained within the normal range despite the presence of significant LV dilatation. Given that severe LV dilatation in asymptomatic patients with AR is an indication for valve replacement this finding significantly limits the ability of normal plasma BNP concentrations to provide reassurance that surgery is not indicated in patients with AR. This finding is in keeping with previous studies which found that

although plasma BNP concentrations increase with AR severity, patients with severe AR and ventricular dilatation have wide range (1.2pg/mL to 200pg/mL) of plasma BNP concentrations with a median BNP concentration of 13.1 pg/mL [Ozkan *et al* 2005]. Although we also found an association with BNP and markers of AR severity we did not find an association between plasma BNP concentrations and any marker of LV size or function at rest. In contrast there was a modest association between plasma BNP concentrations and LA size.

However higher plasma concentrations of BNP were associated with signs of early LV dysfunction immediately post-exercise assessed using speckle tracking derived strain. In particular global longitudinal strain and the change in global longitudinal strain post-exercise was lower in AR patients who had elevated BNP concentrations than those with normal BNP. Despite this there was no statistically significant difference in exercise capacity between AR patients with a normal BNP compared to those with an elevated BNP.

8.3.4 NATRIURETIC PEPTIDES IN DIFFERENT VALVE LESIONS

Unsurprisingly given the differing haemodynamic effects between valve lesions there was a wide range of LV volumes between groups with many patients having evidence of adverse cardiac remodelling. Despite this there was no association between markers of LV size and function for any individual valve lesion. In contrast however, there was an association between plasma BNP and LA size in all valve lesions. Whilst there was also an association with elevated pulmonary artery pressures, the higher pulmonary artery pressure is probably a reflection of the

increased LA pressure. Although BNP release from the RV is also a possibility there were no associations with BNP and markers of RV size or function. This suggests that LA wall stretch may be an important factor in BNP release in VHD. This hypothesis is supported by evidence of synthesis of BNP by atrial myocytes [Langenickel *et al* 2000] and co-storage of BNP with ANP in atrial granules [Goetze *et al* 2006].

There were only a small number of mildly symptomatic patients within this study and of those patients with symptoms few had evidence of severe valve disease at rest. Although the presence of symptoms based on clinical assessment was associated with poorer exercise capacity on exercise testing, there was considerable overlap in keeping with the difficulties in accurately assessing symptom status. In addition although patients with elevated BNP also had objective evidence of exercise limitation, these were not necessarily the ones that were deemed to be symptomatic at rest. This suggests that BNP does offer complementary information to the standard assessment of patients with VHD and that the finding of elevated plasma BNP concentrations in an otherwise asymptomatic patient should prompt further investigation.

8.4 CLINICAL IMPLICATIONS

The findings of this study suggest that the current assessment of patients with VHD remains imperfect. A number of patients that are classified as asymptomatic and remain under routine follow up based on standard assessment criteria have

significantly abnormal findings on exercise echocardiography and/or elevations of BNP. These patients appear to be an increased risk of complication and may benefit from early surgery.

Consequently routine measurement of plasma BNP concentrations and performing regular exercise echocardiography may help identify patients at increased risk. This research suggests that measurement of BNP and exercise echocardiography should form part of the routine assessment of patients with VHD and perhaps be given greater emphasis in clinical guidelines. However further research is required to further define the role of both measurement of plasma BNP concentrations and exercise echocardiography in the assessment of valvular heart disease.

8.5 FUTURE DIRECTIONS

The finding of this study suggest that both BNP and exercise echocardiography have a potential role in the assessment of valvular heart disease. The major limitations of this study are the relatively small number of patients within each valve group and the lack of repeated BNP measurement. Further investigation in this field is on-going.

8.5.1 NATRIURETIC PEPTIDES IN MITRAL REGURGITATION

In addition to our work, other investigators have been assessing the role of natriuretic peptides in VHD. Pizarro et al studied a large cohort of asymptomatic patients with severe organic mitral regurgitation [Pizarro *et al* 2009]. The assessment of MR severity was performed in a similar manner to our study. They followed patients for

up to 4 years with an end point of death, symptoms of heart failure of LV dysfunction. In the initial derivation cohort they identified a value of 105 pg/mL as having the highest sensitivity and specificity for identifying patients with adverse outcome. This finding was then confirmed in the remaining patients who served as a validation cohort.

Pizarro's findings in a larger cohort of MR patients suggest that there may be a stronger role for BNP in valvular heart disease than our findings. However the cut off level of 105 pg/mL is much higher than we observed in our patients with MR. In addition they deemed patients who were referred for surgery as not meeting the endpoint unless there was evidence of LV dysfunction or heart failure. Crucially however Pizarro et al did repeat BNP levels 1 year later and a significant finding was that patients whose plasma BNP concentration became elevated during follow-up were at increased risk of meeting the clinical end point.

8.5.2 REPEATED SAMPLING OF NATRIURETIC PEPTIDES

In our study we were only able to sample BNP at a single time point. Although we found considerable variation in BNP concentrations between patients with seemingly similar severity of VHD, what happens to an individual patients plasma BNP concentration over time is perhaps more important than how it compares to a population of VHD patients. Indeed it is known that in congestive cardiac failure BNP levels fall with treatment and a failure for this to do so is a marker of adverse prognosis. Consequently one area for future investigation would be to take serial

measurements of BNP as part of routine follow up and compare this to repeated objective measures of exercise capacity and clinical outcome.

8.5.3 ASSESSMENT OF VALVE LESION SEVERITY DURING EXERCISE

As discussed previously the worsening of mitral regurgitation with exercise [Magne *et al* 2010] and the increase in Doppler gradients in AS [Marechaux *et al* 2010] have been associated with adverse outcome and provided increased predictive value compared to standard exercise criteria alone. In order to be reliable these studies need to be performed on a semi-supine cycle ergonometer. This remains an uncommon stress modality outside mainland Europe with relatively few centres in the United Kingdom, New Zealand or United States of America using this routinely. However this is changing and any future studies should seek to include this information in the adverse markers of prognosis identified in this study. In addition the ability to acquire images during exercise will facilitate the acquisition of images for strain analysis.

8.5.4 TIMING OF SURGERY

In this study the patients' plasma BNP concentration was not available to the cardiologist caring for the patient. In addition although on ethical grounds any significant adverse findings on treadmill exercise were communicated to the cardiologist, the information from the exercise stress echocardiogram was not routinely used to guide decision-making in the time to referral for valve surgery. The next stage of work would be to determine if the routine incorporation of BNP and

exercise stress echocardiography can guide clinicians in deciding when to consider surgery and improve outcome.

8.5.5 FURTHER PLANNED RESEARCH

Based on our findings we are planning to further investigate the role of both exercise echocardiography and measurement of plasma BNP concentrations. We propose to incorporate exercise stress echocardiography and measurement of plasma BNP concentrations in patients undergoing follow-up in dedicated valve clinics in the Liverpool region. Plasma BNP concentrations will be measured 6 monthly and exercise echocardiography will be performed 12 monthly unless the clinical status of the patient requires this to be done more frequently. Exercise echocardiography will be performed on a semi-supine cycle ergometer with images acquired for the estimation of global longitudinal strain and worsening of valve severity with exercise in addition to the standard echocardiographic markers of severity and adverse features defined by this study. In addition exercise echocardiography and measurement of BNP will be obtained 6 months following valve surgery. Their outcomes will be compared to a cohort of patients undergoing conventional follow up.

8.6 CONCLUSION

This research has highlighted the known difficulties in managing patients with severe valvular heart disease. Although the presence of symptoms are a vital component in contemporary guidelines for the management of VHD, this research has

demonstrated that assessment of symptomatic status can be unreliable. In particular many patients deemed to be asymptomatic had extremely poor exercise capacity on objective exercise echocardiography. In addition the presence of adverse features markers such as reduced exercise capacity (<METS), pulmonary hypertension post exercise (PAP>60 mmHg) and a failure to augment systolic blood pressure (BP rise<20 mmHg) are associated with poor prognosis. These markers are relatively easy to obtain and this research suggests that exercise echocardiography should be used much more frequently in the assessment of VHD and perhaps even incorporated into routine clinical practice.

The role of measuring plasma natriuretic peptide concentrations in VHD remains more uncertain. Although elevated plasma BNP concentrations are associated with some markers of increased severity such as increased pulmonary artery pressure, increased left atrial size and reduced exercise capacity, the association is not robust enough to use natriuretic peptides to exclude haemodynamically significant VHD. However there may remain a role for the use of natriuretic peptides on an individual patient basis rather than across a study population. In particular unexplained high plasma BNP concentrations or a BNP that is rising during follow-up could suggest the need to reassess valve severity. Further work in this area is required and is a target for future research within our department.

BIBLIOGRAPHY

ABSTRACTS

1. **Sharma V**, Kerr AJ, Lee M, Gabriel R, Van Pelt NC, Raffel OC, Stewart RAH. Brain type natriuretic peptide increases with left atrial size but not left ventricular remodelling in both aortic and mitral valve disease. *European Heart Journal* 2010: 31, 469

2. **Sharma V**, Kerr AJ, Raffel OC, Wong SP, White J, Stewart, RAH. BNP predicts exercise time, mitral valve area and left atrial pathology in mitral stenosis. *European Heart Journal* 2006: 27 211

3. **Sharma V**, Raffel OC, Kerr AJ, Wong SP, White J, Oldfield M, Whalley G, Stewart RAH. Mitral annular tissue Doppler imaging is abnormal in patients with mitral stenosis with normal left ventricular ejection fraction. *Heart, Lung and Circulation* 2006: 15 229

4. **Sharma V**, Kerr AJ, Stewart RAH, Wong SP, White J, Oldfield M, Whalley G, Raffel OC. The rise in natriuretic peptide levels with exercise is predictive of increased mitral valve gradients in patients with mitral stenosis. *Heart, Lung and Circulation* 2006: 15 26

5. Park R, Kerr AJ, **Sharma V**, Oldfield M, Stewart RAH, Raffel C. Elevated BNP and right heart function in mitral regurgitation: an exercise stress echo study. *Heart, Lung and Circulation* 2006: 15 239

6. **Sharma V**, Kerr AJ, Raffel OC, Wong SP, White J, Stewart RAH. BNP predicts exercise time, mitral valve area and left atrial pathology in mitral stenosis. *Heart, Lung and Circulation* 2006: 15 226

7. Kerr AJ, Pasupati S, Zeng I, Van Pelt NC, Gabriel RS, **Sharma V**, Raffel OC, Stewart RAH. Do changes in B type natriuretic peptide after symptom limited exercise reflect impaired cardiac function? *Heart Lung and Circulation* 2008: 17 (2) 19

PAPERS

1. Gabriel RS, Kerr AJ, **Sharma V**, Zeng I, Stewart RAH. B- type Natriuretic peptide and left ventricular dysfunction on exercise echocardiography in patients with chronic aortic regurgitation. Heart 2008: 94(7): 897-902.

2. **Sharma V**, Stewart RAH, Lee M, Gabriel R, Van Pelt N, Newby DE and Kerr AJ. Plasma brain natriuretic peptide concentrations in patients with valvular heart disease. *(Open Heart – In Press)*

3. **Sharma V**, Kerr AJ, Irene Zeng, Raffel C, Stewart RAH. Comparison of atrial and brain natriuretic peptide for the assessment of mitral stenosis. Heart, Lung, Circulation 2011: 20:517–524

4. **Sharma V**, Newby DE, Stewart RAH, Lee M, Gabriel, Van Pelt N and Kerr AJ. Exercise echocardiography in patients with valvular heart disease *(Echo Research and Practice* 2015;2(3):89-98. doi:10.1530/ERP-15-0015.

AWARDS

1. **Sharma V**, Kerr AJ, Raffel OC, Wong SP, White J, Stewart, RAH. BNP predicts exercise time, mitral valve area and left atrial pathology in mitral stenosis. Cardiac Society of Australia and New Zealand Annual Meeting. Investigator Of The Year Award 2006.

REFERENCES

Agnoletti G, Rodella A, Ferrari R, Harris P. Release of atrial natriuretic peptide-like immunoreactive material during stretching of the rat atrium in vitro. J Mol Cell Cardiol. 1987;19(3):217-20.

Agricola E, Galderisi M, Oppizzi M, Schinkel AF, Maisano F, De Bonis M, et al. Pulsed tissue Doppler imaging detects early myocardial dysfunction in asymptomatic patients with severe mitral regurgitation. Heart. 2004;90(4):406-10.

Alborino D, Hoffmann JL, Fournet PC, Bloch A. Value of exercise testing to evaluate the indication for surgery in asymptomatic patients with valvular aortic stenosis. J Heart Valve Dis. 2002;11(2):204-9.

Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. Heart. 2001;86(4):381-6.

Anand IS, Fisher LD, Chiang YT, Latini R, Masson S, Maggioni AP, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation. 2003;107(9):1278-83.

Arat-Ozkan A, Kaya A, Yigit Z, Balci H, Okcun B, Yazicioglu N, et al. Serum N-terminal pro-BNP levels correlate with symptoms and echocardiographic findings in patients with mitral stenosis. Echocardiography. 2005;22(6):473-8.

Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr. 2009;10(1):1-25.

Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr. 2009;22(1):1-23; quiz 101-2.

Bekeredjian R, Grayburn PA. Valvular heart disease: aortic regurgitation. Circulation. 2005;112(1):125-34.

Bonow RO, Carabello BA, Kanu C, de Leon AC, Jr., Faxon DP, Freed MD, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart

disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2006;114(5):e84-231.

Bonow RO, Carabello BA, Kanu C, de Leon AC, Jr., Faxon DP, Freed MD, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation. 2006;114(5):e84-231.

Borer JS, Hochreiter C, Herrold EM, Supino P, Aschermann M, Wencker D, et al. Prediction of indications for valve replacement among asymptomatic or minimally symptomatic patients with chronic aortic regurgitation and normal left ventricular performance. Circulation. 1998;97(6):525-34.

Carpentier A. Cardiac valve surgery--the "French correction". J Thorac Cardiovasc Surg. 1983;86(3):323-37.

Cho GY, Chan J, Leano R, Strudwick M, Marwick TH. Comparison of two-dimensional speckle and tissue velocity based strain and validation with harmonic phase magnetic resonance imaging. Am J Cardiol. 2006;97(11):1661-6.

Coutance G, Le Page O, Lo T, Hamon M. Prognostic value of brain natriuretic peptide in acute pulmonary embolism. Critical care. 2008;12(4):R109.

Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. Eur Heart J. 2005;26(13):1309-13.

de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med. 2001;345(14):1014-21.

Dehmer GJ, Firth BG, Hillis LD, Corbett JR, Lewis SE, Parkey RW, et al. Alterations in left ventricular volumes and ejection fraction at rest and during exercise in patients with aortic regulation. Am J Cardiol. 1981;48(1):17-27.

Delahaye JP, Gare JP, Viguier E, Delahaye F, De Gevigney G, Milon H. Natural history of severe mitral regurgitation. Eur Heart J. 1991;12 Suppl B:5-9.

Detaint D, Messika-Zeitoun D, Avierinos JF, Scott C, Chen H, Burnett JC, Jr., et al. B-type natriuretic peptide in organic mitral regurgitation: determinants and impact on outcome. Circulation. 2005;111(18):2391-7.

Detaint D, Messika-Zeitoun D, Chen HH, Rossi A, Avierinos J-F, Scott C, et al. Association of B-type natriuretic peptide activation to left ventricular end-systolic remodeling in organic and functional mitral regurgitation. American Journal of Cardiology. 2006;97(7):1029-34.

Dickstein K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: application of natriuretic peptides. Reply. Eur Heart J. 2008.

Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008;10(10):933-89.

Dillingham MA, Anderson RJ. Inhibition of vasopressin action by atrial natriuretic factor. Science. 1986;231(4745):1572-3.

DuBois D, DuBois EF. Clinical Calorimetry: Tenth Paper a Formula to Estimate the Approximate Surface Area if Height and Weight Be Known. Archives of Internal Medicine. 1916;17(6_2):863.

Dujardin KS, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB, Tajik AJ. Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. Circulation. 1999;99(14):1851-7.

Dussaule JC, Vahanian A, Michel PL, Soullier I, Czekalski S, Acar J, et al. Plasma atrial natriuretic factor and cyclic GMP in mitral stenosis treated by balloon valvulotomy. Effect of atrial fibrillation. Circulation. 1988;78(2):276-85.

Eimer MJ, Ekery DL, Rigolin VH, Bonow RO, Carnethon MR, Cotts WG. Elevated B-type natriuretic peptide in asymptomatic men with chronic aortic regurgitation and preserved left ventricular systolic function. Am J Cardiol. 2004;94(5):676-8.

Engelmann MDM, Niemann L, Kanstrup I-L, Skagen K, Godtfredsen J. Natriuretic peptide response to dynamic exercise in patients with atrial fibrillation. Int J Cardiol. 2005;105(1):31-9.

Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet. 2009;373(9672):1382-94.

Enriquez-Sarano M, Bailey KR, Seward JB, Tajik AJ, Krohn MJ, Mays JM. Quantitative Doppler assessment of valvular regurgitation. Circulation. 1993;87(3):841-8.

Enriquez-Sarano M, Miller FA, Jr., Hayes SN, Bailey KR, Tajik AJ, Seward JB. Effective mitral regurgitant orifice area: clinical use and pitfalls of the proximal isovelocity surface area method. J Am Coll Cardiol. 1995;25(3):703-9.

Eryol NK, Dogan A, Ozdogru I, Inanc MT, Kaya MG, Kalay N. The relationship between the level of plasma B-type natriuretic peptide and mitral stenosis. Int J Cardiovasc Imaging. 2007;23(5):569-74.

Ferrari R, Agnoletti G. Atrial natriuretic peptide: its mechanism of release from the atrium. International Journal of Cardiology. 1989;25(Supplement 1):S3-S15.

Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards. A statement for healthcare professionals from the American Heart Association. Writing Group. Circulation. 1995;91(2):580-615.

Fried TA, McCoy RN, Osgood RW, Stein JH. Effect of atriopeptin II on determinants of glomerular filtration rate in the in vitro perfused dog glomerulus. Am J Physiol. 1986;250(6 Pt 2):F1119-22.

Gabriel RS, Kerr AJ, Sharma V, Zeng IS, Stewart RA. B-type natriuretic peptide and left ventricular dysfunction on exercise echocardiography in patients with chronic aortic regurgitation. Heart. 2008;94(7):897-902.

Galasko GI, Lahiri A, Barnes SC, Collinson P, Senior R. What is the normal range for N-terminal pro-brain natriuretic peptide? How well does this normal range screen for cardiovascular disease? Eur Heart J. 2005;26(21):2269-76.

Gerber IL, Stewart RA, French JK, Legget ME, Greaves SC, West TM, et al. Associations between plasma natriuretic peptide levels, symptoms, and left

ventricular function in patients with chronic aortic regurgitation. Am J Cardiol. 2003;92(6):755-8.

Gerber IL, Stewart RA, Legget ME, West TM, French RL, Sutton TM, et al. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. Circulation. 2003;107(14):1884-90.

Goetze JP, Friis-Hansen L, Rehfeld JF, Nilsson B, Svendsen JH. Atrial secretion of B-type natriuretic peptide. Eur Heart J. 2006;27(14):1648-50.

Goetze JP, Friis-Hansen L, Rehfeld JF, Nilsson B, Svendsen JH. Atrial secretion of B-type natriuretic peptide. Eur Heart J. 2006;27(14):1648-50.

Haluska BA, Short L, Marwick TH. Relationship of ventricular longitudinal function to contractile reserve in patients with mitral regurgitation. Am Heart J. 2003;146(1):183-8.

Harris PJ, Thomas D, Morgan TO. Atrial natriuretic peptide inhibits angiotensin-stimulated proximal tubular sodium and water reabsorption. Nature. 1987;326(6114):697-8.

Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. Circulation. 1979;60(5):1096-104.

Hatle L, Brubakk A, Tromsdal A, Angelsen B. Noninvasive assessment of pressure drop in mitral stenosis by Doppler ultrasound. Br Heart J. 1978;40(2):131-40.

Himelman RB, Stulbarg M, Kircher B, Lee E, Kee L, Dean NC, et al. Noninvasive evaluation of pulmonary artery pressure during exercise by saline-enhanced Doppler echocardiography in chronic pulmonary disease. Circulation. 1989;79(4):863-71.

Himelman RB, Stulbarg MS, Lee E, Kuecherer HF, Schiller NB. Noninvasive evaluation of pulmonary artery systolic pressures during dynamic exercise by saline-enhanced Doppler echocardiography. Am Heart J. 1990;119(3 Pt 1):685-8.

Horstkotte D, Loogen F. The natural history of aortic valve stenosis. Eur Heart J. 1988;9 Suppl E:57-64.

Iltumur K, Karabulut A, Yokus B, Yavuzkir M, Taskesen T, Toprak N. N-terminal proBNP plasma levels correlate with severity of mitral stenosis. J Heart Valve Dis. 2005;14(6):735-41.

Ishikura F, Nagata S, Akaike M, Tamai J, Miyatake K. Effects of percutaneous transvenous mitral commissurotomy on levels of plasma atrial natriuretic peptide during exercise. Am J Cardiol. 1991;67(1):74-8.

Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003;24(13):1231-43.

Johnson LL, Powers ER, Tzall WR, Feder J, Sciacca RR, Cannon PJ. Left ventricular volume and ejection fraction response to exercise in aortic regurgitation. Am J Cardiol. 1983;51(8):1379-85.

Kerr AJ, Raffel OC, Whalley GA, Zeng I, Stewart RA. Elevated B-type natriuretic peptide despite normal left ventricular function on rest and exercise stress echocardiography in mitral regurgitation. Eur Heart J. 2008;29(3):363-70.

Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. J Am Coll Cardiol. 1997;30(3):746-52.

Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. Circulation. 2005;112(9 Suppl):I377-82.

Lancellotti P, Moonen M, Magne J, O'Connor K, Cosyns B, Attena E, et al. Prognostic effect of long-axis left ventricular dysfunction and B-type natriuretic peptide levels in asymptomatic aortic stenosis. Am J Cardiol. 2010;105(3):383-8.

Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-63.

Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of

Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. Journal of the American Society of Echocardiography. 2005;18(12):1440-63.

Langenickel T, Pagel I, Hohnel K, Dietz R, Willenbrock R. Differential regulation of cardiac ANP and BNP mRNA in different stages of experimental heart failure. Am J Physiol Heart Circ Physiol. 2000;278(5):H1500-6.

Lee R, Haluska B, Leung DY, Case C, Mundy J, Marwick TH. Functional and prognostic implications of left ventricular contractile reserve in patients with asymptomatic severe mitral regurgitation. Heart. 2005;91(11):1407-12.

Lee R, Hanekom L, Marwick TH, Leano R, Wahi S. Prediction of subclinical left ventricular dysfunction with strain rate imaging in patients with asymptomatic severe mitral regurgitation. Am J Cardiol. 2004;94(10):1333-7.

Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. Am J Cardiol. 1999;84(7):829-32.

Leung DY, Griffin BP, Stewart WJ, Cosgrove DM, 3rd, Thomas JD, Marwick TH. Left ventricular function after valve repair for chronic mitral regurgitation: predictive value of preoperative assessment of contractile reserve by exercise echocardiography. J Am Coll Cardiol. 1996;28(5):1198-205.

Levin ER, Gardner DG, Samson WK. Natriuretic peptides. New England Journal of Medicine. 1998;339(5):321-8.

Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med. 1998;339(5):321-8.

Light DB, Schwiebert EM, Karlson KH, Stanton BA. Atrial natriuretic peptide inhibits a cation channel in renal inner medullary collecting duct cells. Science. 1989;243(4889):383-5.

Magne J, Lancellotti P, Pierard LA. Exercise-induced changes in degenerative mitral regurgitation. J Am Coll Cardiol. 2010;56(4):300-9.

Magne J, Mahjoub H, Dulgheru R, Pibarot P, Pierard LA, Lancellotti P. Left ventricular contractile reserve in asymptomatic primary mitral regurgitation. Eur Heart J. 2014;35(24):1608-16.

Marechaux S, Bellouin A, Polge AS, Richardson-Lobbedez M, Lubret R, Asseman P, et al. Clinical value of exercise Doppler echocardiography in patients with cardiac-valvular disease. Archives of cardiovascular diseases. 2008;101(5):351-60.

Marechaux S, Hachicha Z, Bellouin A, Dumesnil JG, Meimoun P, Pasquet A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. Eur Heart J. 2010;31(11):1390-7.

Marin-Grez M, Fleming JT, Steinhausen M. Atrial natriuretic peptide causes pre-glomerular vasodilatation and post-glomerular vasoconstriction in rat kidney. Nature. 1986;324(6096):473-6.

Martin RP, Rakowski H, Kleiman JH, Beaver W, London E, Popp RL. Reliability and reproducibility of two dimensional echocardiograph measurement of the stenotic mitral valve orifice area. Am J Cardiol. 1979;43(3):560-8.

Marwick TH. Measurement of strain and strain rate by echocardiography: ready for prime time? J Am Coll Cardiol. 2006;47(7):1313-27.

McCully RB, Roger VL, Mahoney DW, Burger KN, Click RL, Seward JB, et al. Outcome after abnormal exercise echocardiography for patients with good exercise capacity: prognostic importance of the extent and severity of exercise-related left ventricular dysfunction. J Am Coll Cardiol. 2002;39(8):1345-52.

McDonagh TA, Cunningham AD, Morrison CE, McMurray JJ, Ford I, Morton JJ, et al. Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population. Heart. 2001;86(1):21-6.

McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet. 1998;351(9095):9-13.

Messika-Zeitoun D, Johnson BD, Nkomo V, Avierinos JF, Allison TG, Scott C, et al. Cardiopulmonary exercise testing determination of functional capacity in mitral regurgitation: physiologic and outcome implications. J Am Coll Cardiol. 2006;47(12):2521-7.

Metra M, Nodari S, Parrinello G, Specchia C, Brentana L, Rocca P, et al. The role of plasma biomarkers in acute heart failure. Serial changes and independent prognostic value of NT-proBNP and cardiac troponin-T. Eur J Heart Fail. 2007;9(8):776-86.

Moura LM, Ramos SF, Pinto FJ, Barros IM, Rocha-Goncalves F. Analysis of variability and reproducibility of echocardiography measurements in valvular aortic valve stenosis. Rev Port Cardiol. 2011;30(1):25-33.

Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol. 1997;30(6):1527-33.

Nakamura M, Kawata Y, Yoshida H, Arakawa N, Koeda T, Ichikawa T, et al. Relationship between plasma atrial and brain natriuretic peptide concentration and hemodynamic parameters during percutaneous transvenous mitral valvulotomy in patients with mitral stenosis. American Heart Journal. 1992;124(5):1283-8.

Nakatani S, Masuyama T, Kodama K, Kitabatake A, Fujii K, Kamada T. Value and limitations of Doppler echocardiography in the quantification of stenotic mitral valve area: comparison of the pressure half-time and the continuity equation methods. Circulation. 1988;77(1):78-85.

Nessmith MG, Fukuta H, Brucks S, Little WC. Usefulness of an Elevated B-Type Natriuretic Peptide in Predicting Survival in Patients With Aortic Stenosis Treated Without Surgery. The American Journal of Cardiology. 2005;96(10):1445-8.

Nishikimi T, Kohno M, Matsuura T, Akioka K, Teragaki M, Yasuda M, et al. Effect of exercise on circulating atrial natriuretic polypeptide in valvular heart disease. The American Journal of Cardiology. 1986;58(11):1119-20.

Nishikimi T, Kohno M, Matsuura T, Akioka K, Teragaki M, Yasuda M, et al. Effect of exercise on circulating atrial natriuretic polypeptide in valvular heart disease. Am J Cardiol. 1986;58(11):1119-20.

Nishimura RA, Carabello BA, Faxon DP, Freed MD, Lytle BW, O'Gara PT, et al. ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2008;118(8):887-96.

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57-185.

Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005-11.

Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG, et al. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. J Am Coll Cardiol. 2005;45(12):2034-41.

Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. Br Heart J. 1962;24:349-57.

Omland T, Aakvaag A, Bonarjee VV, Caidahl K, Lie RT, Nilsen DW, et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction. Comparison with plasma atrial natriuretic peptide and N-terminal proatrial natriuretic peptide. Circulation. 1996;93(11):1963-9.

Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation. 2000;102(15):1788-94.

Otto CM. Textbook of Clinical Echocardiography. 2nd ed. Philadelphia: W.B. Saunders; 2000.

Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. Circulation. 1997;95(9):2262-70.

Ozkan M, Baysan O, Erinc K, Koz C, Yokusoglu M, Uzun M, et al. Brain natriuretic peptide and the severity of aortic regurgitation: is there any correlation? The Journal of international medical research. 2005;33(4):454-9.

Paraskevaidis IA, Tsiapras D, Kyrzopoulos S, Cokkinos P, Iliodromitis EK, Parissis J, et al. The role of left ventricular long-axis contraction in patients with asymptomatic aortic regurgitation. J Am Soc Echocardiogr. 2006;19(3):249-54.

Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation. 2005;111(24):3290-5.

Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation. 2009;119(7):1034-48.

Pizarro R, Bazzino OO, Oberti PF, Falconi M, Achilli F, Arias A, et al. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. J Am Coll Cardiol. 2009;54(12):1099-106.

Prasad N, Bridges AB, Lang CC, Clarkson PB, MacLeod C, Pringle TH, et al. Brain natriuretic peptide concentrations in patients with aortic stenosis. Am Heart J. 1997;133(4):477-9.

Qi W, Mathisen P, Kjekshus J, Simonsen S, Bjornerheim R, Endresen K, et al. Natriuretic peptides in patients with aortic stenosis. Am Heart J. 2001;142(4):725-32.

Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr. 2002;15(2):167-84.

Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA, Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of E. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Journal of the American Society of Echocardiography. 2002;15(2):167-84.

Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC, Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol. 2002;40(5):976-82.

Reis G, Motta MS, Barbosa MM, Esteves WA, Souza SF, Bocchi EA. Dobutamine stress echocardiography for noninvasive assessment and risk stratification of patients with rheumatic mitral stenosis. J Am Coll Cardiol. 2004;43(3):393-401.

Richards AM, Nicholls MG, Yandle TG, Frampton C, Espiner EA, Turner JG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. Circulation. 1998;97(19):1921-9.

Richards AM, Nicholls MG, Yandle TG, Ikram H, Espiner EA, Turner JG, et al. Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction. The Christchurch Cardioendocrine Research Group. Heart. 1999;81(2):114-20.

Rodeheffer RJ. Measuring plasma B-type natriuretic peptide in heart failure: good to go in 2004? J Am Coll Cardiol. 2004;44(4):740-9.

Ross J, Jr., Braunwald E. Aortic stenosis. Circulation. 1968;38(1 Suppl):61-7.

Schuler G, von Olshausen K, Schwarz F, Mehmel H, Hofmann M, Hermann HJ, et al. Noninvasive assessment of myocardial contractility in asymptomatic patients with sever aortic regurgitation and normal left ventricular ejection fraction at rest. Am J Cardiol. 1982;50(1):45-52.

Schulz-Knappe P, Forssmann K, Herbst F, Hock D, Pipkorn R, Forssmann WG. Isolation and structural analysis of "urodilatin", a new peptide of the cardiodilatin-(ANP)-family, extracted from human urine. Klinische Wochenschrift. 1988;66(17):752-9.

Selcuk MT, Selcuk H, Maden O, Erbay AR, Temizhan A, Aksu T, et al. The effect of percutaneous balloon mitral valvuloplasty on N-terminal- pro B- type natriuretic peptide plasma levels in mitral stenosis. Int Heart J. 2007;48(5):579-90.

Sharma V, Stewart RA, Zeng I, Raffel C, Kerr AJ. Comparison of atrial and brain natriuretic peptide for the assessment of mitral stenosis. Heart Lung Circ. 2011;20(8):517-24.

Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999;83(6):897-902.

Sonnenberg H, Honrath U, Chong CK, Wilson DR. Atrial natriuretic factor inhibits sodium transport in medullary collecting duct. Am J Physiol. 1986;250(6 Pt 2):F963-6.

Stockand JD, Sansom SC. Regulation of filtration rate by glomerular mesangial cells in health and diabetic renal disease. American journal of kidney diseases : the official journal of the National Kidney Foundation. 1997;29(6):971-81.

Sutton TM, Stewart RA, Gerber IL, West TM, Richards AM, Yandle TG, et al. Plasma natriuretic peptide levels increase with symptoms and severity of mitral regurgitation. J Am Coll Cardiol. 2003;41(12):2280-7.

Thomas L, Foster E, Hoffman JI, Schiller NB. The Mitral Regurgitation Index: an echocardiographic guide to severity. J Am Coll Cardiol. 1999;33(7):2016-22.

Thompson CA, Jabbour S, Goldberg RJ, McClean RY, Bilchik BZ, Blatt CM, et al. Exercise performance-based outcomes of medically treated patients with coronary artery disease and profound ST segment depression. J Am Coll Cardiol. 2000;36(7):2140-5.

Thompson R, Ross I, Leslie P, Easthope R. Haemodynamic adaptation to exercise in asymptomatic patients with severe aortic regurgitation. Cardiovasc Res. 1985;19(4):212-8.

Tsai RC, Yamaji T, Ishibashi M, Takaku F, Fu M, Cherng WJ, et al. Atrial natriuretic peptide and vasopressin during percutaneous transvenous mitral valvuloplasty and relation to renin-angiotensin-aldosterone system and renal function. Am J Cardiol. 1990;65(13):882-6.

Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J. 2007;28(2):230-68.

Van Pelt NC, Kerr AJ, Legget ME, Pasupati S, Whalley G, Wong S, et al. Increased B-type natriuretic peptide is associated with an abnormal blood pressure response to exercise in asymptomatic aortic stenosis. Int J Cardiol. 2008;127(3):313-20.

Van Pelt NC, Stewart RAH, Legget ME, Whalley GA, Wong SP, Zeng I, et al. Longitudinal left ventricular contractile dysfunction after exercise in aortic stenosis. Heart. 2007;93(6):732-8.

Vinereanu D, Ionescu AA, Fraser AG. Assessment of left ventricular long axis contraction can detect early myocardial dysfunction in asymptomatic patients with severe aortic regurgitation. Heart. 2001;85(1):30-6.

Wahi S, Haluska B, Pasquet A, Case C, Rimmerman CM, Marwick TH. Exercise echocardiography predicts development of left ventricular dysfunction in medically and surgically treated patients with asymptomatic severe aortic regurgitation. Heart. 2000;84(6):606-14.

Weber M, Arnold R, Rau M, Brandt R, Berkovitsch A, Mitrovic V, et al. Relation of N-terminal pro-B-type natriuretic peptide to severity of valvular aortic stenosis. Am J Cardiol. 2004;94(6):740-5.

Weber M, Arnold R, Rau M, Elsaesser A, Brandt R, Mitrovic V, et al. Relation of N-terminal pro B-type natriuretic peptide to progression of aortic valve disease. Eur Heart J. 2005;26(10):1023-30.

Wood P. An appreciation of mitral stenosis. I. Clinical features. Br Med J. 1954;1(4870):1051-63; contd.

Yandle TG, Richards AM, Gilbert A, Fisher S, Holmes S, Espiner EA. Assay of brain natriuretic peptide (BNP) in human plasma: evidence for high molecular weight BNP as a major plasma component in heart failure. Journal of Clinical Endocrinology & Metabolism. 1993;76(4):832-8.

Yandle TG, Richards AM, Gilbert A, Fisher S, Holmes S, Espiner EA. Assay of brain natriuretic peptide (BNP) in human plasma: evidence for high molecular weight BNP as a major plasma component in heart failure. J Clin Endocrinol Metab. 1993;76(4):832-8.

Yoshimura M, Yasue H, Okumura K, Ogawa H, Jougasaki M, Mukoyama M, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. Circulation. 1993;87(2):464-9.

Yusoff R, Clayton N, Keevil B, Morris J, Ray S. Utility of plasma N-terminal brain natriuretic peptide as a marker of functional capacity in patients with chronic severe mitral regurgitation. Am J Cardiol. 2006;97(10):1498-501.

Zamorano J, Cordeiro P, Sugeng L, Perez de Isla L, Weinert L, Macaya C, et al. Real-time three-dimensional echocardiography for rheumatic mitral valve stenosis evaluation: an accurate and novel approach. J Am Coll Cardiol. 2004;43(11):2091-6.

Zeidel ML. Regulation of collecting duct Na+ reabsorption by ANP 31-67. Clin Exp Pharmacol Physiol. 1995;22(2):121-4.

Zeidel ML, Kikeri D, Silva P, Burrowes M, Brenner BM. Atrial natriuretic peptides inhibit conductive sodium uptake by rabbit inner medullary collecting duct cells. J Clin Invest. 1988;82(3):1067-74.

Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003;16(7):777-802.

Appendix 1.1

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

Date of Visit: ___ ___ / ___ ___ ___ / ___ ___ ___ ___

SECTION 1: DEMOGRAPHIC

Date of Birth: ___ ___ / ___ ___ ___ / ___ ___ ___ ___ **Gender:** ❑ **Male** ❑ **Female**

Ethnic Origin:

- ❑ NZ European
- ❑ Other European
- ❑ NZ Maori
- ❑ Pacific Island
- ❑ Chinese
- ❑ Indian
- ❑ Other Asian
- ❑ Middle Eastern
- ❑ Latin American/Hispanic
- ❑ African
- ❑ Other
- ❑ Not stated

SECTION 2: ETIOLOGY OF CARDIOVASCULAR DISEASE

Age cardiac disease first diagnosed: _____ years

Degenerative
↘ ❑ Yes ❑ No

Congenital
↘ ❑ Yes ❑ No

Rheumatic
↘ ❑ Yes ❑ No

↘ **If yes:** Age at last acute rheumatic fever:___ years Comments: _____

Marfan's
↘ ❑ Yes ❑ No

Connective tissue disease
↘ ❑ Yes ❑ No

↘ **If yes:** Please specify: _____

Previous endocarditis
↘ ❑ Yes ❑ No

Aortic root dilatation
↘ ❑ Yes ❑ No

Appendix 1.2

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

SECTION 2: ETIOLOGY CARDIOVASCULAR DISEASE (CONTINUED)

Other

↘ ❑ Yes ❑ No

↘ **If yes:** Please specify: _____

Previous mitral valvotomy

↘ ❑ Yes ❑ No

↘ **If yes:** ❑ Balloon ❑ Open

Please specify date of last procedure: ___ ___ / ___ ___ ___ / ___ ___ ___ ___

SECTION 3: PHYSICAL

Height: _____cm **Weight:** _____kg **BSA**: _____ m^2 **Blood Pressure:** ____ / ____ mmHg

Appendix 1.3

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

SECTION 4: HISTORY

Please note: this question refers to any previous history.

4.1. Heart Failure:

NYHA Class ❑ 1 ❑ 2 ❑ 3 ❑ 4 Current NYHA Class ❑ 1 ❑ 2 ❑ 3 ❑ 4

↘ If NYHA Class ≥ 2: Are symptoms due to cardiac cause?

↘ ❑ Unlikely ❑ Unsure ❑ Likely ↘ ❑ Unlikely ❑ Unsure ❑ Likely

Hospital admission with heart failure

↘ ❑ Yes ❑ No

↘ **If yes:** Date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___

Medical treatment for heart failure

↘ ❑ Yes ❑ No Current ↘ ❑ Yes ❑ No

History of paroxysmal nocturnal dyspnoea or orthopnoea

↘ ❑ Yes ❑ No Current ↘ ❑ Yes ❑ No

Left ventricular failure on chest X-ray

↘ ❑ Yes ❑ No Current ↘ ❑ Yes ❑ No

↘ **If yes:** Date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___

4.2. Myocardial Ischaemia:

Angina

↘ ❑ Yes ❑ No

↘ **If yes:** CCS Class ❑ 1 ❑ 2 ❑ 3 ❑ 4

Troponin Positive Acute Coronary Syndrome

↘ ❑ Yes ❑ No

↘ **If yes:** Date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___

Coronary angiography

↘ ❑ Yes ❑ Not done

↘ **If yes:** ❑ Normal ❑ CAD (≥ 50% coronary stenosis)

Percutaneous coronary intervention

↘ ❑ Yes ❑ No

Appendix 1.4

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

SECTION 4: HISTORY (CONTINUED)

4.3. Arrhythmias:

Palpitations
↘ ❑ Yes ❑ No

Paroxysmal atrial fibrillation/flutter
↘ ❑ Yes ❑ No

Persistent atrial fibrillation/flutter
↘ ❑ Yes ❑ No

Non sustained ventricular tachycardia
↘ ❑ Yes ❑ No

Sustained ventricular tachycardia
↘ ❑ Yes ❑ No

Ventricular fibrillation
↘ ❑ Yes ❑ No

DC Cardioversion
↘ ❑ Yes ❑ No

4.4. Other:

Transient ischaemic attack
↘ ❑ Yes ❑ No

Stroke
↘ ❑ Yes ❑ No

Other systemic thrombo-embolism
↘ ❑ Yes ❑ No

Haemoptysis
↘ ❑ Yes ❑ No

4.5. Syncope:
↘ ❑ Yes ❑ No

Pre-syncope (≥ 2 episodes)
↘ ❑ Yes ❑ No

Appendix 1.5

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

SECTION 4: HISTORY (CONTINUED)

4.6. Other problems:

Hypertension
↘ ❑ Yes ❑ No

Diabetes Mellitus
↘ ❑ Yes ❑ No

COAD
↘ ❑ Yes ❑ No

Smoker
↘ ❑ Current ❑ Never ❑ Past

SECTION 5: CURRENT MEDICAL PROBLEMS (not documented above)

Has the patient suffered a significant medical problem or is patient currently (< 2 weeks) unwell?

❑ Yes ❑ No → *Go to section 6.*

↘ If yes list diseases below*:	Severity:**	ICD Code
_____	❑ Mild ❑ Moderate ❑ Severe	_____
_____	❑ Mild ❑ Moderate ❑ Severe	_____
_____	❑ Mild ❑ Moderate ❑ Severe	_____
_____	❑ Mild ❑ Moderate ❑ Severe	_____
_____	❑ Mild ❑ Moderate ❑ Severe	_____

** Please do not include conditions which cause minor disability and have resolved for > 2 weeks.*

*** Definitions of severity:*

Mild	*Causing no limitation of usual activities.*
Moderate	*Causing some limitation of usual activities.*
Severe	*Causing inability to carry out usual activities.*

Appendix 1.6

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

SECTION 6: CURRENT MEDICATIONS

6.1. Current Cardiovascular Medications: ❑ Yes ❑ No→ *Go to Question 6.2.*

↘ If yes:		Generic Name	Dose
Ace Inhibitor ↘ ❑ Yes ❑ No	↘ **If yes:**	_____	_____tab/mg/day
Angiotensin II Receptor Blocker ↘ ❑ Yes ❑ No	↘ **If yes:**	_____	_____mg/day
Beta Blocker ↘ ❑ Yes ❑ No	↘ **If yes:**	_____	_____mg/day
Loop Diuretic ↘ ❑ Yes ❑ No	↘ **If yes:**	_____	_____tab/mg/day

Alpha Blocker	↘ ❑ Yes	❑ No
Antiarrhythmic	↘ ❑ Yes	❑ No
Aspirin	↘ ❑ Yes	❑ No
Calcium Antagonist	↘ ❑ Yes	❑ No
Clopidogrel	↘ ❑ Yes	❑ No
Digoxin	↘ ❑ Yes	❑ No
Nitrates	↘ ❑ Yes	❑ No

Appendix 1.7

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

SECTION 6: CURRENT MEDICATIONS (continued)

Dipyridamole
↘ ❑ Yes ❑ No

Spironolactone
↘ ❑ Yes ❑ No

Statin
↘ ❑ Yes ❑ No

Thiazide Diuretic
↘ ❑ Yes ❑ No

6.2. Current Non-Cardiac Medications:

Anti Inflammatory
↘ ❑ Yes ❑ No

Corticosteroids
↘ ❑ Yes ❑ No

Hormone Replacement Therapy
↘ ❑ Yes ❑ No

Immunosuppressive Drug
↘ ❑ Yes ❑ No

Insulin
↘ ❑ Yes ❑ No

Warfarin
↘ ❑ Yes ❑ No

Appendix 1.8

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

SECTION 7: ACTIVITY QUESTIONNAIRE

Please enter data provided by the patient.

Date of Completion *(by the patient)*: __ __ / __ __ __ / __ __ __ __

7.1. In general, how is the patient's health now? *Please tick one.*

- Excellent ❑
- Very Good ❑
- Good ❑
- Fair ❑
- Poor ❑

7.2. Compared to 6 months ago, how is the patient's general health rated now? *Please tick one.*

- Much better now ❑
- Somewhat better now ❑
- About the same ❑
- Somewhat worse now ❑
- Much worse now ❑

7.3. During the past 6 months has the patient had any of the following problems as a result of his/her physical health? *Please tick one per line.*

		Yes	No
a.	Cut down on the amount of time he/she spent on work or other activities.	❑	❑
b.	Accomplished less than he/she would like	❑	❑
c.	Were limited in the kind of work or other activities	❑	❑
d.	Had difficulty performing work or other activities (for example, it took extra effort)	❑	❑

Appendix 1.9

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

SECTION 7: ACTIVITY QUESTIONNAIRE (continued)

7.4. The following questions are about activities the patient might do during a typical day. Does his/her health now limit him/her in these activities? If so, how much? *Please tick one box per line.*

	Limited a lot	Limited a little	Not limited
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	❑	❑	❑
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	❑	❑	❑
c. Lifting or carrying groceries	❑	❑	❑
d. Climbing several flights of stairs	❑	❑	❑
e. Climbing one flight of stairs	❑	❑	❑
f. Bending, kneeling or stooping	❑	❑	❑
g. Walking more than one kilometre	❑	❑	❑
h. Walking half a kilometre	❑	❑	❑
i. Walking 100 metres	❑	❑	❑
j. Bathing or dressing yourself	❑	❑	❑

7.5. Are the patient's activities limited by any of the following? *Please tick one box per line.*

	Yes	No
a. Shortness of breath	❑	❑
b. Chest discomfort or tightness (angina)	❑	❑
c. Dizziness	❑	❑
d. Fatigue or tiredness	❑	❑
e. Arthritis or muscle weakness	❑	❑
f. Other	❑	❑

Appendix 1.10

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

SECTION 8: LABORATORY DATA

Date of blood samples: ___ ___ / ___ ___ ___ / ___ ___ ___ ___

	Result	Normal Range
Haemoglobin	___ ___ ___ g / L	_____
Haematocrit	___ . ___ ___L / L	_____
White Cell Count	___ ___ . ___ ___ $x10^9$/L	_____
Creatinine	___ . ___ ___ mmol/L	_____
CRP	___ ___ ___ . ___ mg/L	_____
ESR	___ ___ ___	_____

Study blood sample analysed at CHCH Cardio Endocrine Laboratory:

Baseline # MS.__ __ __ , BMV # MS.__ __ __ , Post procedure # MS.__ __ __

Has the patient consented:

Yes	No	
❑	❑	Sending blood overseas
❑	❑	Long term storage
❑	❑	Future testing
❑	❑	Stress test

SECTION 9: PROCEDURES

ECG completed: ❑ Yes ❑ No **Date completed:** ___ ___ / ___ ___ ___ / ___ ___ ___ ___

2D Echo completed: ❑ Yes ❑ No **Date completed:** ___ ___ / ___ ___ ___ / ___ ___ ___ ___

ESE completed: ❑ Yes ❑ No **Date completed:** ___ ___ / ___ ___ ___ / ___ ___ ___ ___

Appendix 1.11

Site : _____

Patient Study # : ___ ___ . ___ ___

Patient Initials: ___ ___ ___

BASELINE CASE REPORT FORM

SECTION 10: PLAN FOR FOLLOW-UP

Site of clinical f/u : _____

Follow up date: __ __ / __ __ / __ __

Date form completed: ___ ___ / ___ ___ ___ / ___ ___ ___ ___

Form completed by: _____
(Please print name)

Signature: _____

Appendix 2.1

CONFIDENTIAL

Aortic Regurgitation
Exercise Echocardiography Worksheet

Hospital Sticker
(Patient Details)

Patient study #: **AR** __ __ , **ENP.** __ __ __

Date of Echo: __ __ / __ __ __ / __ __ __ __

Disc No: …… , Tape No: ……

General	
1. ❑	**Label Recording** include patient initials, date of birth, study number (if available), and date of echo
2. ❑	**Synchronise clocks of Echo machine and Exercise machine**

ECHOCARDIOGRAPHY VIEWS (2 loops minimum in SR 4 for AF for each)

Purpose	View	Comments
BASELINE		
• Chamber dimensions • Chamber dimension • LVOT dimension • AR/MR • AR Severity • AR Severity	**Parasternal Long Axis Views** ❑ 2D PLAX View ❑ M-Mode Ao/LA and LV ❑ Zoom LVOT ❑ Colour Aortic and Mitral Valves ❑ Colour M-mode LVOT ❑ Colour AV for vena contracta	
• AV morphology • AR severity • LV function	**Parasternal Short Axis view** ❑ PSAX AoV ❑ Colour PSAX AoV ❑ PSAX LV base/mid LV/apex	
• LA/RA area • LV volume • LA Volume • MR severity • Diastolics • AR continuity • AR continuity • Aortic valve • AR Severity • AS • AS/AR Severity • TR Severity • PA pressure • PA pressure • Strain • LV volumes	**Apical Views** ❑ 2D 4C all chambers ❑ 2D Zoom 4 Ch LV ❑ 2D 2Ch LA/LV ❑ 2D 4C Colour MV ❑ PW MV Tips ❑ PW MV Annulus ❑ 2D Zoom MV annulus ❑ 2D 5C view ❑ Colour AoV ❑ PW LVOT ❑ CW AoV for AR P 1/2 Time ❑ Colour Tricuspid Valve ❑ CW Tricuspid Valve AP4 and RVOT ❑ CW Tricuspid Valve with saline contrast ❑ Colour TVI –(3 loops, increase FR) ❑ Triplane LV	

Appendix 2.2

CONFIDENTIAL

Aortic Regurgitation
Exercise Echocardiography Worksheet

Hospital Sticker
(Patient Details)

Patient study #: **AR** __ __ , **ENP.** __ __ __

Date of Echo: __ __ / __ __ __ / __ __ __ __

Disc No: ……. , Tape No: …….

General	
1. ❑	**Label Recording** include patient initials, date of birth, study number (if available), and date of echo
2. ❑	**Synchronise clocks of Echo machine and Exercise machine**

ECHOCARDIOGRAPHY VIEWS (2 loops minimum in SR 4 for AF for each)

Purpose	View	Comments	
	BASELINE		
	Tissue Doppler		
• LV diastolics	❑ TVI lateral and Medial Mitral valve		
• RV function	❑ TVI lateral Tricuspid Valve		
	Subcostal View		
• RA pressure	❑ IVC		
• AR Severity	❑ Colour Abdo Aorta		
• AR Severity	❑ PW Abdo Aorta		
	Suprasternal View		
• AR Severity	❑ PW descending aorta		
• AR Severity	❑ Colour descending aorta		
	Femoral View		
• AR Severity	❑ 2D Colour Femoral artery		
• AR Severity	❑ PW Femoral Artery		
	POST EXERCISE: 0 min	**5 min**	**10 min**
	Parasternal Short Axis view		
• Chamber Volumes	❑ AP 4C View		
• PA pressure	❑ CW tricuspid Valve		
• PA pressure	❑ CW Tricuspid valve with saline		
• Tissue Doppler	❑ TVI Medial and Lateral MV		
• Tissue Doppler	❑ TVI lateral Tricuspid Valve		
	Femoral View		
• AR Severity	❑ 2D Colour Femoral Artery		
• AR Severity	❑ PW Femoral Artery		

Comments: _____
_____
_____

Appendix 3

Exercise Natriuretic Peptides & Mitral Stenosis: Exercise Test CRF

Date __ __/__ __/__ __ __ __

MS Biomarker # MS . __ __
ENP# ENP . __ __ __
Initials: __ __ __
Site:

Patient details

D.O.B __ __ /__ __/__ __ __ __ , Sex M ☐ F ☐

Height __ __ __ . __ cm, Weight __ __ __ . __ kg, BSA __ __ . __ __

Blood samples

1. Baseline sample time __ __ : __ __ # ENP__ __ __A

2. Exercise sample time __ __ : __ __ # ENP__ __ __B
time __ __ : __ __ # ENP__ __ __C
time __ __ : __ __ # ENP__ __ __D
time __ __ : __ __ # ENP__ __ __E

Exercise test

Protocol: Bruce std ☐ , Bruce mod ☐ _____

Duration of exercise __ __ min __ __ sec METS __ __ . __

Start time __ __.__ __.__ __ , End time __ __.__ __.__ __

Max pred HR __ __ __ bpm, Max HR achieved __ __ __ bpm, % __ __ . __

Stage/time	Base/00:00	2min :	5min :	8min :	11min :	14min :	17min :
HR	L S						
BP	L S						

Rhythm: Baseline subjective NYHA: ___ Objective ETT NYHA: ___ (METS:__)

Comments: _____
_____
_____

Echocardiogram

Disc No: __ __ __ __ __ __ Tape No: __ __ __ __ __ Echo/**ETT** clock sync: __ __ __ __ __

Appendix 4

CONFIDENTIAL

Mitral Stenosis
Exercise Echocardiography Worksheet

Hospital Sticker
(Patient Details)

Patient study #: **MS.__ __** , **ENP. __ __ __**

Date of Echo: __ __ / __ __ __ / __ __ __ __

Disc No: …… , Tape No: ……..

General		
1.	❑	**Label Recording** include patient initials, date of birth, study number (if available), and date of echo
2.	❑	**Synchronise clocks of Echo machine and Exercise machine**

ECHOCARDIOGRAPHY VIEWS (2 loops minimum in SR 4 for AF for each)

Purpose		**View**	**Comments**	
		BASELINE		
		Apical Views		
1	Chamber volume	❑ 2D 4C all chambers		
2	Mitral valve gradients	❑ CW mitral inflow		
3	PA pressure *	❑ CW tricuspid valve		
4	PA pressure *	❑ CW tricuspid valve with saline contrast		
5	TVI of Right ventricle	❑ Tissue Doppler of RV		
		Parasternal View RVOT		
6	PA pressure *	❑ CW tricuspid valve		
7	PA pressure *	❑ CW tricuspid valve with saline contrast		
		Subcostal View		
7	RA pressure	❑ IVC and hepatic veins		
7	RA pressure	❑ IVC and hepatic veins		
		**** Use view with best assessment of PA pressure at Baseline to do PA pressure post Exercise***		
		POST EXERCISE: 0 min	**5 min**	**10 min**
		Apical Views time __ __:__ __	__ __:__ __	__ __:__ __
8	Chamber volume	❑ 2D 4C all chambers	❑	❑
9	Mitral valve gradients	❑ CW mitral inflow	❑	❑
10	PA pressure *	❑ CW tricuspid valve	❑	❑
11	PA pressure *	❑ CW tricuspid valve with saline contrast	❑	❑
		Parasternal View RVOT		
12	PA pressure *	❑ CW tricuspid valve	❑	❑
13	PA pressure *	❑ CW tricuspid valve with saline contrast	❑	❑
14	PA pressure *	CW tricuspid valve with saline contrast	❑	❑
		Apical View		
15	TVI of Right ventricle	❑ Tissue Doppler of RV	❑	❑

Comments: _____

_____

_____

Appendix 5

WE ARE SEEKING HEALTHY VOLUNTEERS FOR A CARDIOLOGY RESEARCH PROJECT AT MIDDLEMORE HOSPITAL

WOULD YOU LIKE TO DO AN EXERCISE STRESS ECHOCARDIOGRAM??

ARE YOU RELATIVELY HEALTHY??

FOR MORE INFORMATION, PLEASE CONTACT

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Appendix 6 Exercise protocol for use in valvular heart disease. peak exercise capacity at the end of each 3 minute stage is similar to that of the BRUCE protocol.

VALVE PROTOCOL				**BRUCE PROTOCOL**				**Total Time**
	Time in Stage	Speed (Km/h)	Grade(%)		Time in Stage	Speed (Km/h)	Grade (%)	(mins)
Stage 1	01:00	1.8	3					01:00
Stage 2	01:00	2.1	6					02:00
Stage 3	01:00	2.7	10	Stage 1	03:00	2.7	10	03:00
Stage 4	01:00	3.1	11					04:00
Stage 5	01:00	3.5	12					05:00
Stage 6	01:00	4	13	Stage 2	03:00	4	12	06:00
Stage 7	01:00	4.3	14					07:00
Stage 8	01:00	5	14					08:00
Stage 9	01:00	5.3	15	Stage 3	03:00	5.4	14	09:00
Stage 10	01:00	5.8	16					10:00
Stage 11	01:00	6.4	16					11:00
Stage 12	01:00	6.8	17	Stage 4	03:00	6.7	16	12:00